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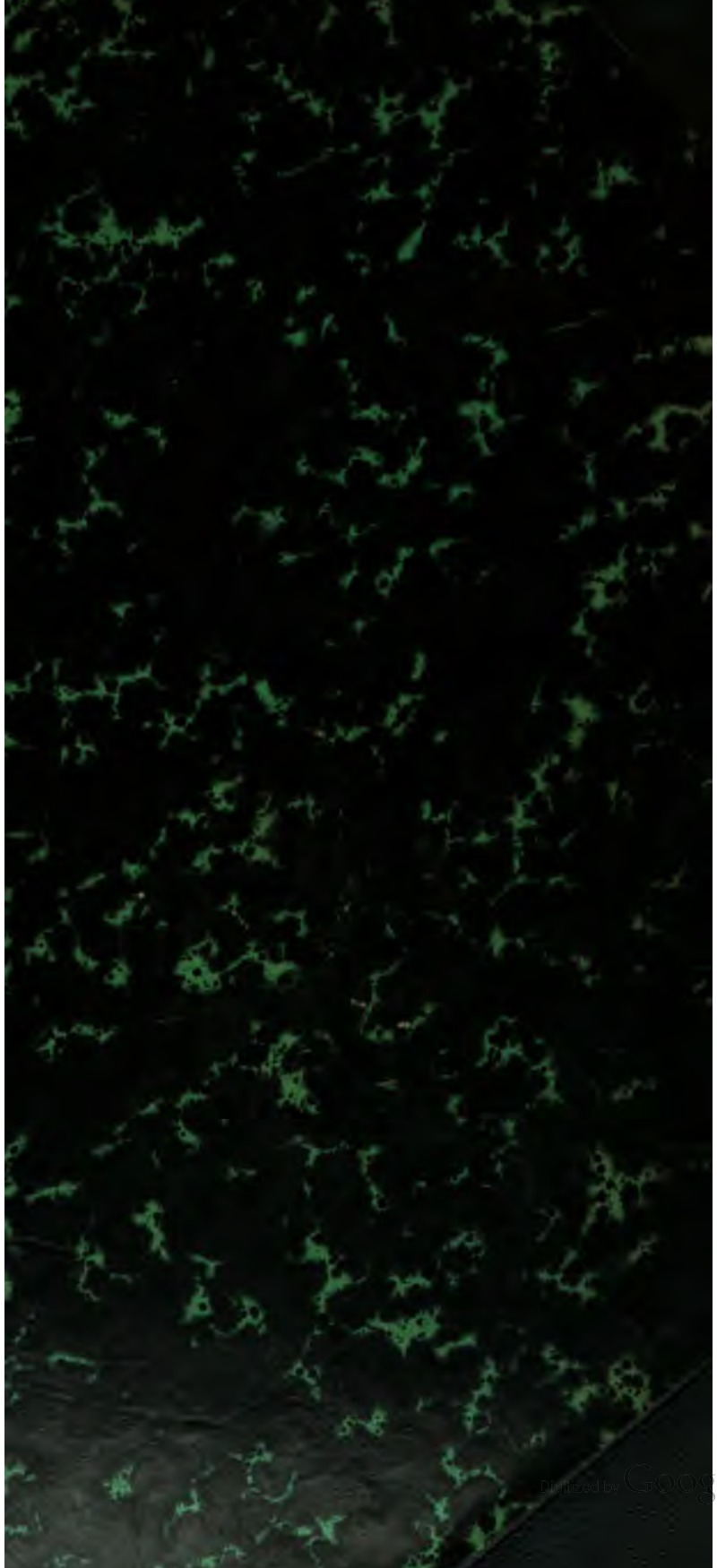
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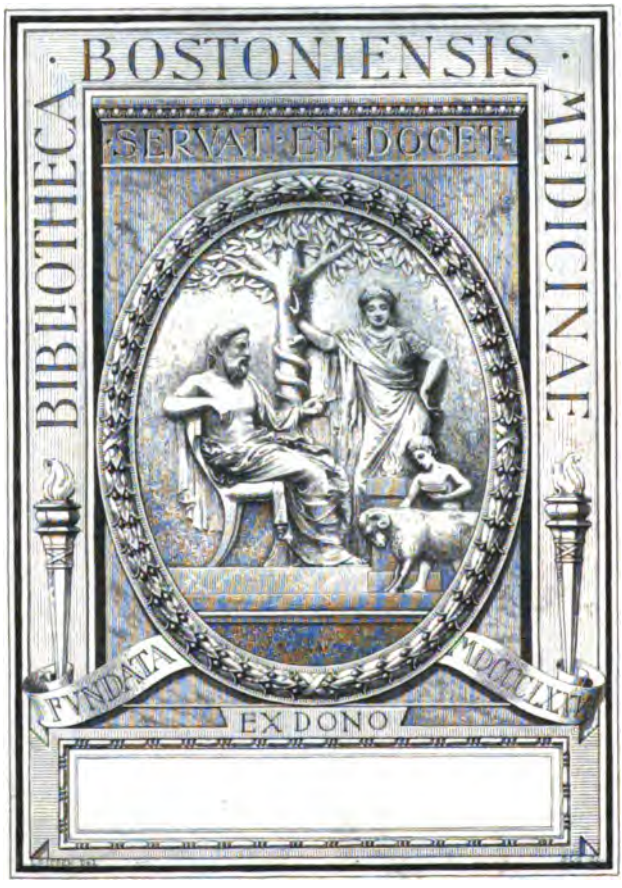

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MEDICAL PAPERS

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REGINALD HEBER FITZ

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TO

REGINALD HEBER FITZ, M.D., LL.D.

HERSEY PROFESSOR OF THE THEORY AND PRACTICE OF PHYSIC
IN HARVARD UNIVERSITY

FROM

HIS FORMER HOUSE PUPILS AT THE MASSACHUSETTS
GENERAL HOSPITAL AND ASSISTANTS IN THE
DEPARTMENT OF THE THEORY AND
PRACTICE OF PHYSICS, HAR-
VARD UNIVERSITY

IN HONOR OF HIS SIXTY-FIFTH BIRTHDAY
MAY 5, 1908

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REGINALD HEBER FITZ.

REGINALD HEBER FITZ, whose house officers and assistants have united to celebrate his sixty-fifth birthday, has for thirty-eight years been an active factor in the development of medicine and medical education, not only in Boston, but also in the United States. Having graduated from Harvard in 1864, Dr. Fitz started his medical studies in Cambridge under the inspiring direction of the eminent physician and anatomist, Jeffries Wyman. At the same time he attended the lectures at the Harvard Medical School. The following year he came to Boston and devoted himself to study at the Medical School until April, 1867, when he became house officer at the Boston City Hospital. Here, during the service of Dr. John G. Blake, he had an opportunity to study a severe epidemic of typhus fever. After the hospital service, a few months sufficed to give him his degree, and at the end of his four years of medical training, soon after commencement, in 1868, he sailed for Europe.

Virchow had published his "Cellular Pathology" ten years before, and during the time that had elapsed the men who were to make modern medicine had developed under the inspiration of this truly epoch-making man and were in a position to give their best teaching. In Vienna under

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Oppolzer and Skoda, in Berlin under Virchow, in Paris under Cornil and in London under Murchison, Dr. Fitz studied and worked. Before his return to Boston in 1870, he published a paper in Virchow's *Archives* on "Bronchiectasis."

Coming back to Boston from his period of close application in the European laboratories, his ability and attainments were at once recognized, especially by the older and powerful group of men at the Massachusetts General Hospital and the Harvard Medical School, so that in 1871 he was made Microscopist to the former and at the latter Instructor in Pathological Anatomy. His methodical German methods at autopsies were a revelation to the house officers of that day, and he early demonstrated his skill as a microscopist by making, in a tumor of doubtful origin, a correct diagnosis of syphilis, to the discomfiture of his competitors in microscopic work.

Two years later, in 1873, he entered the faculty of the Harvard Medical School as Assistant Professor of Pathology, so that for thirty-five years he has had to do constructively with medical education.

Dr. Fitz's return to Boston, it will be remembered, was coincident with Charles W. Eliot's advent to the presidency of Harvard College. President Eliot had immediately joined the radicals of the medical faculty, and aided them in putting through the changes which did away with the old lecture system and established the first graded course of medical instruction in the coun-

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try. Although Dr. Fitz took no part in bringing about this change in the course of study, nevertheless as secretary of the faculty from 1874 to 1883 he did much towards setting forth the advantages of the graded continuous course of study, so that one by one the other schools of the country fell into line. He early became a member of the committee of the faculty on the course of study. and for many years has acted as chairman of this committee. In this position he has exerted an influence on medical education by many carefully considered reports which he has presented to the faculty.

As we have seen, Dr. Fitz early took rank as a pathologist, but at the same time he held the position as physician at the Boston Dispensary from 1871 to 1882, and he has, throughout his career, looked upon pathology and allied medical sciences as the handmaidens of clinical medicine rather than goddesses to be pursued for their own charms.

Dr. Fitz was appointed Professor of Pathological Anatomy in 1878, the title being changed to Shattuck Professor of Pathological Anatomy the following year. His lectures were descriptions of the changes found in regions and organs rather than of the processes bringing about the changes. The causal factors in disease were but dimly understood until the later days of his professorship, but his clear-cut, concise description of pathological changes will ever remain with his pupils.

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In 1886 he presented, at the meeting of the Association of American Physicians, his most celebrated contribution to medical literature, entitled, " Perforating Inflammation of the Vermiform Appendix, with Special Reference to its Early Diagnosis and Treatment."

In the following year, 1887, he was appointed one of the Visiting Physicians of the Massachusetts General Hospital, though he maintained his position of professor of pathological anatomy at the Medical School till 1892, when he became Hersey Professor of the Theory and Practice of Physic. In this position he made no attempt to modify the old lecture system of this professorship beyond the establishment of his famous quiz-clinic, where the students' reasoning faculties were sharpened under the watchful eye of the professor himself. In his lectures selected groups of diseases were treated so that the student might have a comprehensive grasp of the underlying pathological conditions on which the whole group were dependent.

In 1900, urged on by the great development in the knowledge of disease processes and of laboratory methods for the recognition of morbid conditions, Dr. Fitz found it necessary to introduce into his department a body of assistants who should aid in the work. This group of men have taught in small sections, giving in the second year the most elementary instruction, which is supplemented in the third year by more advanced work. This system of teaching he expanded until now

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in the fourth year there are courses in the hospital wards and laboratories where patients are under continuous observation by the students. Opportunity is also offered at the Medical School for original investigation on medical problems, making in all a very comprehensive course of study for the student in the Theory and Practice of Medicine.

In 1889 Dr. Fitz delivered, before the New York Pathological Society, his second notable contribution to medical literature, the Middleton Goldsmith Lecture on " Acute Pancreatitis."

Honors in the medical world have come to Dr. Fitz, and we find that he has had not only membership in the local medical societies, but a guiding hand as well, having served The Massachusetts Medical Society as Councilor for many years, and the Boston Society for Medical Improvement as president. In 1889 he was elected a Fellow of the American Society of Arts and Sciences; in 1892, Associate Fellow of the College of Physicians of Philadelphia; in 1893 Honorary Member of the Medical and Chirurgical Faculty of the State of Maryland; in 1900 Corresponding Member of the Schlesische Gesellschaft für Vaterländische Cultur; in 1904 Honorary Fellow of the New York Academy of Medicine; in 1907 Corresponding Member of Gesellschaft für innere Medicin und Kinderheilkunde of Vienna; in 1905 Harvard College conferred the degree of LL.D.; he was president of the Association of American Physicians in 1894, and in 1907 he was president of the

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Congress of American Physicians and Surgeons, delivering an address entitled the " Borderland of Medicine and Surgery."

The work that Dr. Fitz has done during his active period of life has been largely critical and judicial, though always with a constructive tendency. He has formed his opinions for himself, and then bravely stood by them, even at times when they were in opposition to those of a majority of his friends or to the potent influence of the president of the university. His general position has been that of a conservative and critical councilor rather than a radical leader. His industrious habits of work have been individualistic on the whole. He has studied the works of others, rearranged their ideas or presented them in a new and truer light to the world but has not sought to be the leader of a group of students searching for new facts. Yet his personal industrious application to study has been a source of inspiration to those who have had the good fortune to be his students and assistants.

The freedom from the petty annoyances of teaching and hospital detail that is to come to him is to be considered an earnest of wise and thoughtful articles in the near future on some of the great problems that concern medical advancement.

A. K. Stone.

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Case II. (Chart II.) IVpara, thirty-one years. Five and a half months pregnant.

Family history unimportant.

Measles as a child, otherwise always well.

One child living, four years old. Two miscarriages at seven months, cause unknown. There was nothing in the history to suggest kidney trouble, no headaches, unusual nausea or vomiting, edema, or eye symptoms. Until the present illness began was never up at night to micturate.

Entered St. Elizabeth Hospital Nov. 8, 1907. Five days before complained of pain between shoulders. The next day was in bed because of great weakness. The urine at this time was noticed to be scanty. There was severe headache and a complaint of specks before the eyes. There were no edema, no convulsions.

Physical examination showed nothing remarkable beyond a very high tension pulse (220), a sharply accentuated aortic second sound, and the uterus enlarged to correspond to a pregnancy of about five and one-half months. The urine was diminished in quantity, 850 ccm. in the twenty-four hours; there was a large amount of albumin and many casts, both hyaline and granular.

Under treatment the urine increased to 2,000 ccm., but the blood pressure remained high (225).

Nov. 11, three days after entrance, the eyes were examined and showed the presence of fresh retinal hemorrhages. Labor now began and she delivered herself on Nov. 12. Forty-eight hours after delivery the blood pressure had dropped from 223 to 180, and marked improvement had taken place in the patient's condition. From Nov. 18 to 23 there was a febrile condition without obvious cause, yet during this the blood pressure continued to fall. A complete recovery

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Table of Blood Counts.

	Hb. Per cent.	Erythrocytes.	Leucocytes.	Per cent in count of 200.					Seen in Count		Platelets.	Stippling.	Polychromatophilia.	Poikilocytosis.	Macrocytosis.	Microcytosis.
				Poly. Neut.	Lymph. Large. Small.	Poly. Eos.	Mast cells.	Myelocytes.	Blasts Nor.	Blasts Meg.						
e 1.....	55	2,136,000	3,300	53	45	0	1	1	7	1	diminished	slight	moderate	moderate	little	much
10....	55	2,044,000	4,400	52	48	0	0	0	1	5	rare	none	marked	,,	,,	,,
14....	45	2,580,000	6,000	37.5	59.5	1	0	2	2	2	very rare	slight	,,	,,	,,	,,
y 12	15	1,072,000	14,700	6.5	92.5	1	0	+	6	2	very rare	marked	,,	,,	,,	,,
14	15	816,000	91,500	6.1	92.9 / 84 8.9	0.1	0	0.9	6	9	* ,,	,,	,,	,,	,,	,,

*In count of 1000 whites.

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No case exactly similar to this has been found in the accessible literature. Large hematomata requiring operation are not very rare in severe anemias and leukemias. Milward reports a case in which there were swellings about the knees supposed to be scorbutic; the case afterward proved to be lymphatic leukemia. Barié and Salmon also report a case of enormous hematoma of the shoulder in a case of acute leukemia. The case reported here was at first supposed to be sepsis; this was disproved by microscopic examination of and by cultures from the fluid removed from the swelling; it was then considered to be perhaps a tumor of bone which had undergone degeneration, but neither the appearance of the bone in the neighborhood nor the microscopic examination of the marrow supports this theory. In the absence of a complete autopsy we are again reduced to conjecture, but the cellular elements of the marrow, taken with the blood picture, point to the marrow as the most probable primary seat of disease.

It has been suggested that there was a general hyperplasia of the bone-marrow cells, and that the terminal drain, perhaps of the operation and subsequent oozing, drew out the erythroblasts, platelets and polynuclears into the blood-stream but left the giant cells *in situ* because of some mechanical obstruction. It is undoubtedly true that rapid changes took place in the blood just before death and that a very great increase occurred in the number of circulating polynuclears

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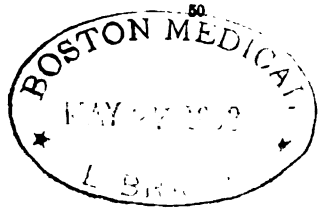
case was a patient with cardiac disease who died shortly after admission; another cardiac case with embolism died after two weeks' stay in the ward, and the last (the seventh) was a patient who had severe myocarditis. The cases of typhoid, twelve in number, all made good recoveries; though several of them were very sick and five had relapses; they seemed to require fewer baths than one would expect in a closed ward. Patients with pleurisy with effusion and tubercular peritonitis, excepting two which were very far advanced, patients with pneumonia, bronchitis, debility and neurasthenia, as would be expected, did remarkably well.

Cases of arthritis were watched with interest, but there were no cases where the course of the disease seemed to be prolonged by the fresh air treatment. The renal and cardiac cases seemed to be benefited by being out-of-doors. Three cases of malaria were admitted and were segregated only by individual mosquito nets, but no case of malaria developed in the ward.

Perhaps the most remarkable clinical fact was the great reduction in the frequency with which hypnotics had to be prescribed, even in the cases where the patients were high-strung, and even the pain due to malignant disease seemed to be controlled by much smaller amounts of analgesics than would ordinarily be expected.

However, the most striking feature was that the patients, all women, and all belonging to the humbler classes, really the most conservative por-



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tissue stroma is present in large amount, and everywhere it is more abundant than in the preceding tumors. (Fig. 5.) Tumor cells here vary more in shape than in the other cases because they frequently appear to be crowded into narrow crevices between connective tissue bundles. Where this is not the case they are oval or polygonal. (Fig. 16.) The cell outline is sharp though there is no indication of a cell membrane. Cytoplasm is homogeneous, very finely granular, at times it is finely vacuolated. Cytoplasm is weakly basophilic. Nuclei are round or oval, sometimes slightly irregular, almost always eccentric in the cell. Chromatin is in fairly fine masses scattered throughout the nucleus, but is relatively not very abundant. There is a slight tendency to peripheral arrangement of chromatin masses. In many nuclei there is a metachromatic nucleolus.

Case VI. Stroma is very slight in amount in this tumor, and appears as a delicate, coarse-meshed reticulum. (Fig. 6.) The tumor cells are of a surprisingly uniform appearance. They are round or oval, frequently polygonal. (Fig. 23.) The cytoplasm is almost homogeneous and has a slight affinity for basic dyes. The nucleus is almost always round and an eccentric position is almost constant. Chromatin masses are relatively large in size, and for the most part lie in close apposition to the cell membrane so that there is left a small central portion rather free from chromatin. In a moderate number of the cells there is a distinct metachromatic nucleolus.

Case VII (University of Buffalo, 2368) [4] was autopsied by Dr. C. A. Bentz, of Buffalo, on Oct. 13, 1904. This was a patient, a male, aged forty-nine years, who

[4] I take pleasure in expressing here my thanks to Dr. Bentz for his courtesy in furnishing this tissue and his permission to use it in this connection.

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had been in good health almost up to the time of his admission to the hospital on July 5, 1904. Three months prior to this time he began to feel severe pain along the course of the sciatic nerves. Previously he had had occasional twinges of pain in the same region. The pain during the three months had grown steadily worse and the patient was confined to bed almost all of the time. The urine examination showed a few hyaline casts and albumin, but no mention is made of the presence of albumose. The autopsy showed cirrhosis of the liver and chronic interstitial nephritis. There were osseous projections laterally from the bodies of the vertebræ and a tumor growth in the sternum and third lumbar vertebra. The tissue from these tumors preserved in formalin was put at my disposal for study.

The tumor is for the most part very cellular, with a small amount of intervening stroma. (Fig. 7.) In other places the cells are separated by a fair amount of connective tissue. Throughout the tumor there are numerous blood vessels of relatively large caliber and thin walls. Many sections show an extensive degree of hemorrhage into the cellular portions of the tumor; this is so marked in places that it gives the appearance of a blood clot, with here and there scattered small groups of tumor cells.

The tumor cells themselves are of a quite uniform appearance, not varying very greatly either in size, in shape or in staining reaction. The contour of the individual cells (Fig. 19) is regular and sharply outlined, but there is no evidence of a distinct cell membrane. The cells are for the most part round or slightly oval. Where they are most crowded together there is a slight tendency to a polygonal shape, and in a few places where stroma is fairly abundant the cells may be squeezed into somewhat irregular shapes. The

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average of a number of measurements of these cells is 9 x 7.7 microns. The cytoplasm of the cells, whether stained with hematoxylin and eosin or with phosphotungstic acid hematoxylin after mordanting with picric acid and ammonium bichromate, is very homogeneous, presenting a ground-glass appearance (Fig. 19), with only an occasional cell that is finely vacuolated. The cytoplasm is distinctly, though moderately, basophilic. The cells in this tumor do not show the ragged, frayed-out edge due to peripheral vacuolization as described in some of the other of these tumors.

In the phosphotungstic acid hematoxylin preparations many of the cells show near the nucleus a distinctly paler zone, near whose center lie two minute dots similar to those described in the preceding tumors and considered to be centrosomes. These dots lie very close together and frequently it is impossible to make out more than one dot. This appearance of a single dot may be due either to the fact that one dot overlies the other dot or to the fact that it is not always possible optically to resolve bodies lying as close together as some of these may.

The nucleus of these cells usually has a distinctly eccentric position in the cell body, and frequently it lies peripherally. (Fig. 19.) The nuclei themselves are round or oval and the average of a number of measurements is 5.3 x 4.6 microns. Occasionally a nucleus has a slightly irregular contour or it may show an indentation of its sides suggesting direct division. Sometimes a nucleus has a pseudopodic projection, but this is not common. Nuclei vary rather more in size than do the cell bodies, still there is no very great irregularity in nuclear structure. The chromatin is present in rather fine masses which show a slight tendency to a peripheral grouping. (Fig. 19.) How-

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ever, this is not marked and there is no definite mural arrangement of the chromatin, though there appears to be a fairly distinct nuclear membrane.

A number of cells show near the center of their nucleus a small, rounded mass tending to stain slightly metachromatically and which may be regarded as a nucleolus. Here again this is not a very marked feature of the tumor, though in some of the cells the mass is very distinct. No mitoses were found in the examination of a large number of fields.

Three variations of the type cell of the tumor occur, but the total number of these cells is very small. Some of the cells have two, three or rarely four, nuclei, with a corresponding increase in the size of the cell body. Other cells have nuclei larger, more deeply staining and slightly more irregular in contour than the type cell. The upper limit of the size of these nuclei is about 2½ times the average nucleus. A moderate number of cells have nuclei which show slight degrees of shrinkage with a diffuse, rather dark staining nucleus (pyknosis). There is no evidence of hemoglobin staining in the tumor cells even where there is marked hemorrhage, and in this respect the tumor differs from most of the preceding ones.

Case VIII (Myeloma "X").[5] Tissue consists of a portion of a rib and part of a nodule adjacent to the rib. Both pieces were preserved in alcohol. There is no bone present in the nodule, whereas tissue from the rib contains bone requiring decalcification with 5% nitric acid before sectioning. This is a cellular tumor with rather more fibrous tissue stroma than was present in many of the other specimens of myeloma. Again, the arrangement of the stroma is rather different from

[5] For this tissue I am indebted to Dr. E. Libman, Mt. Sinai Hospital, New York, to whom I express my thanks. This patient did not come to autopsy.

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most of the other cases in that there are moderately coarse connective tissue bundles forming elongated spaces or meshes in which the cells are closely crowded, with little or no intercellular stroma. (Fig. 8.) Blood vessels for the most part run in these connective tissue bundles and consequently have fairly definite, rather thick walls in comparison with the diameter of the blood vessels themselves. Individual cells vary considerably in shape, depending upon how closely crowded together they are. Where they lie fairly far apart they are for the most part of an irregular, oval shape; sometimes they are round, but more usually they are polygonal, owing to pressure of adjacent cells, but even under these conditions they are very apt to have one diameter longer than the other. (Figs. 14 and 15.) They are of a fairly uniform size, and the average of a number of measurements is 11.2 x 10 microns. The cell outline is almost always distinct, but there is no suggestion of a cell membrane. The cytoplasm is finely granular, of a ground-glass appearance (Fig. 27), but some cells have a slightly more coarsely granular cytoplasm. Occasionally a cell is finely vacuolated. (Fig. 14.) The latter, however, is an infrequent finding and is not sufficient to give the cells the frayed-out ragged border which has been described in several of the other cases. The cytoplasm is distinctly, though not markedly, basophilic. The nucleus very frequently is eccentrically situated, and it is unusual to see the nucleus distinctly centrally placed. (Figs. 14, 15 and 27.)

The nuclei are round to slightly oval and have a distinct outline which may be interpreted as a nuclear membrane. (Fig. 14.) The nuclei vary considerably in size and also in structure. Some of them are distinctly vesicular with fine chromatin granules which

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show a distinct tendency to group themselves peripherally on the nuclear membrane. In others there is very little peripheral grouping of the chromatin. In most of these nuclei, usually somewhat eccentrically placed, though sometimes in the center, there is a distinct, rounded, homogeneous, refractile mass, staining with eosin and averaging 1 micron in diameter, rarely 2 microns. (Fig. 15.) This is interpreted to be a nucleolus. Nuclei of this type average 6.6 x 6.1 microns in diameter.

Another very common type of nucleus is about one half the size of the one previously described, is very much less vesicular, the chromatin granules are coarser or more or less fused together into a diffusely staining mass. This type of nucleus seems to pass by gradual transitions into one still smaller, more homogeneous and more deeply staining, until finally the nucleus is represented by a deeply stained, homogeneous mass, one quarter or less the size of the first described vesicular nucleus. It would seem that this represents a progressive, degenerative change with shrinkage of the nucleus from the original vesicular nucleus. Another very common type of cell has a nucleus no longer vesicular and in which the nuclear material forms itself into six to ten rounded homogeneous, deeply-staining masses varying in size from one to two microns. (Fig. 27.) In a number of these cells the masses group themselves peripherally, and the nucleolus can still be distinguished in the center. However, the nuclear membrane often seems to have disappeared or to be only indefinitely represented. (Fig. 27.) Instead of a nuclear membrane, very frequently there is a pale zone immediately around the nuclear mass, as if this nuclear material lay in a vacuole; and with the peripheral grouping of the globules of nuclear material it frequently pre-

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sents a picture not dissimilar from that shown in certain stages of the segmentation of malarial parasites.

In other cells, with the disappearance of the nuclear membrane, the chromatin masses appear to lie free in the cytoplasm of the cells. In this type of cells the nuclear masses may remain connected to each other by means of a fine thread staining indistinctly with nuclear stains. In some fields of the sections this type of fragmented nucleus is much more abundant than in other fields, though there is no other difference suggestive of a cause for this.

An occasional cell contains two or three nuclei, and in the latter the nuclei may show any of the varieties of structure already described. No positive evidence of mitosis can be found in the cells of this part of the tumor. Sometimes the formation of separate nuclear fragments gives a picture suggestive of some stage of mitosis, but in all cases it seemed that the picture could not justly be interpreted as one of mitosis. These changes are regarded rather as a peculiar form of degeneration, such as has already been described in some of the previous cases. Moreover, there is no indication of indirect division taking place in the cells.

The sections made from portions of the rib and adjacent tissue after decalcification show almost complete disappearance of the marrow and replacement by tumor tissue. Here the tumor does not show the arrangement with coarser bands of connective tissue enclosing groups of tumor cells, but there is a rather more generally distributed connective tissue framework made up of very delicate connective tissue bundles and thin walled, small blood vessels which frequently lie in close apposition to tumor cells. Fragmentation of the nucleus and formation of several small masses of nuclear material do not appear to take place except infre-

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quently in these portions of the tumor. The tumor cells in these sections, however, have the same general characteristics with regard to cytoplasm as described above. Numerous shrunken, more deeply staining nuclei occur as in the adjacent nodule. Mitotic figures occur and are not very infrequent in these sections. The trabeculæ of bone seem to have atrophied to a great extent; the tumor has penetrated the bone in places and infiltrated the adjacent fibrous, adipose and muscular tissue. The distinctly invasive character of the tumor growth is best shown where the tumor has invaded striated muscle and the tumor cells are crowded between the muscle fibers. In a few of the sections the bone marrow is not entirely replaced by the tumor, and tumor cells can be seen scattered singly or in small groups amidst the bone marrow cells. The tumor cells can be easily picked out from the other marrow cells by their larger size, the distinct nucleolus and the fine chromatin granules tending to group themselves on the periphery. No hemoglobin pigmentation of the cells in this tumor can be made out.

Case IX (Buffalo Myeloma, No. 2).[6] This case, a man of forty-nine years, was autopsied Oct. 11, 1907, by Dr. C. A. Bentz, in Buffalo. There were numerous tumors present in the bones of the skull, clavicle, ribs and sternum. The eighth rib on the left side showed a growth the size of an English walnut, which had produced fracture of that bone. The fifth rib on the right side showed a similar tumor. At the junction of the gladiolus and manubrium sterni there was a tumor mass about the size of a dollar, and here the bone also was fractured. At the sterno-clavicular articulation on the right side there is a growth 2½ in. long and 2 in. in

[6] This case was placed at my disposal by Dr. C. A. Bentz, of Buffalo.

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width, which originates in the clavicle and presents on section a mottled gray and red appearance. This bone, too, is fractured. Above the left ear in the skull there is a mass the size of a silver dollar which is soft, with crater-like edges. On the forehead, 3 in. above the right eyebrow, there is a similar mass the size of a hazelnut, and another back of the right ear. The abdominal and thoracic viscera present no abnormalities, and there is no evidence of any metastases beyond the bones.

This tumor is composed almost entirely of cells, among which there are scattered a few connective tissue fibrils forming an ill-defined reticular meshwork. (Fig. 9.) In addition there is a moderate amount of connective tissue accompanying rather large blood vessels, but the walls of the blood vessels for the most part are thin. In some sections, however, there are very large blood vessels with quite thick connective tissue walls containing relatively few cells and no definite muscularis or elastic tissue layer. These areas give the appearance of an angioma made up of rather large venous sinuses, between the walls of which are scattered the myelomatous tumor. Hemorrhagic areas occur quite often.

The cells in this tumor are of quite uniform size. For the most part the cell outline is distinct without there being anything to suggest a cell membrane. (Fig. 21.) The cytoplasm is almost homogeneous or finely granular and has a distinct affinity for basic stains. Some cells show a fine vacuolization of the cytoplasm. The average of a number of measurements is 10.2 x 8.7 microns.

The nuclei most usually have an eccentric position in the cells (Fig. 21), though the cells in proportion to the size of the nucleus are frequently not very large and often one diameter is not very much greater than the

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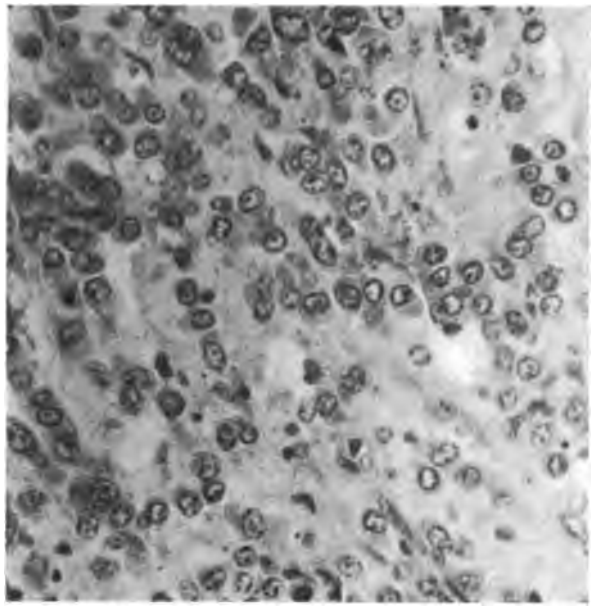

FIG. 1. CASE I.

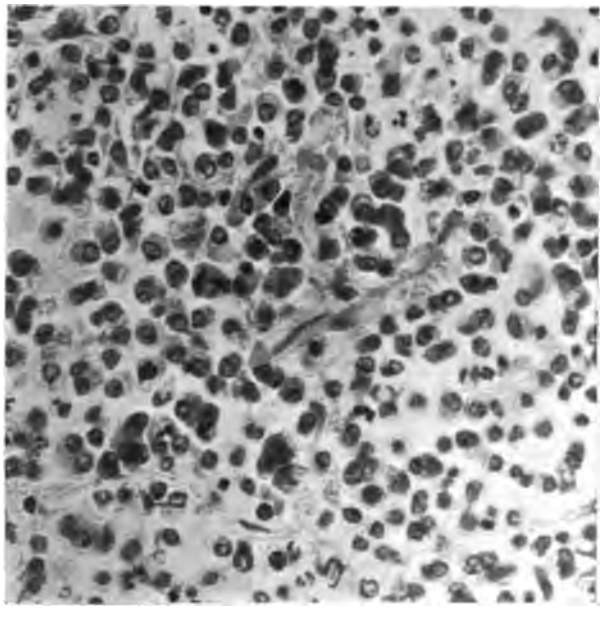

FIG. 2. CASE II.

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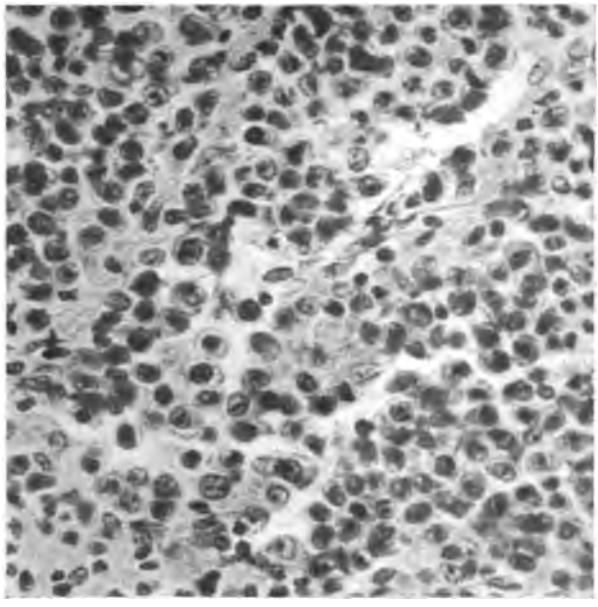

FIG. 3. CASE III.

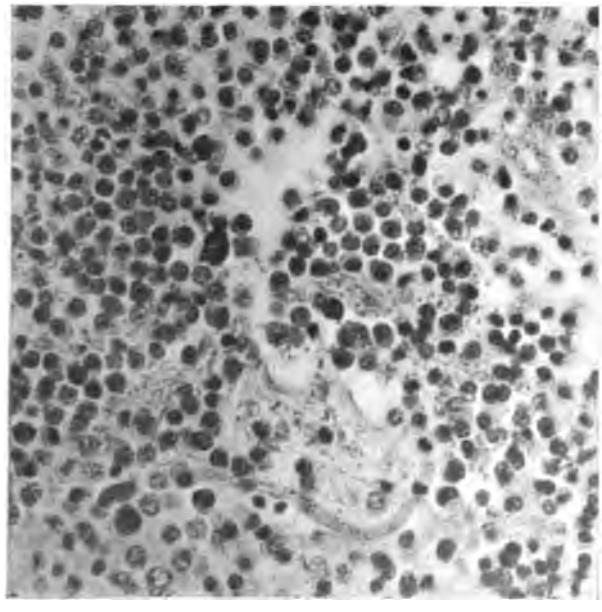

FIG. 4. CASE IV.

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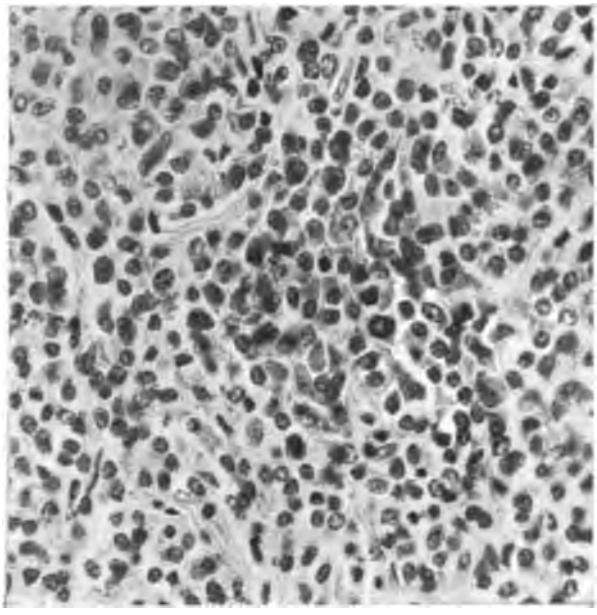

FIG. 5. CASE V.

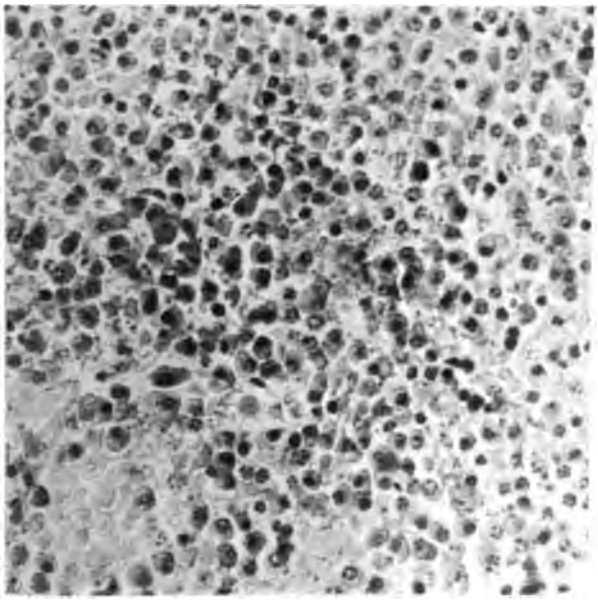

FIG. 6. CASE VI.

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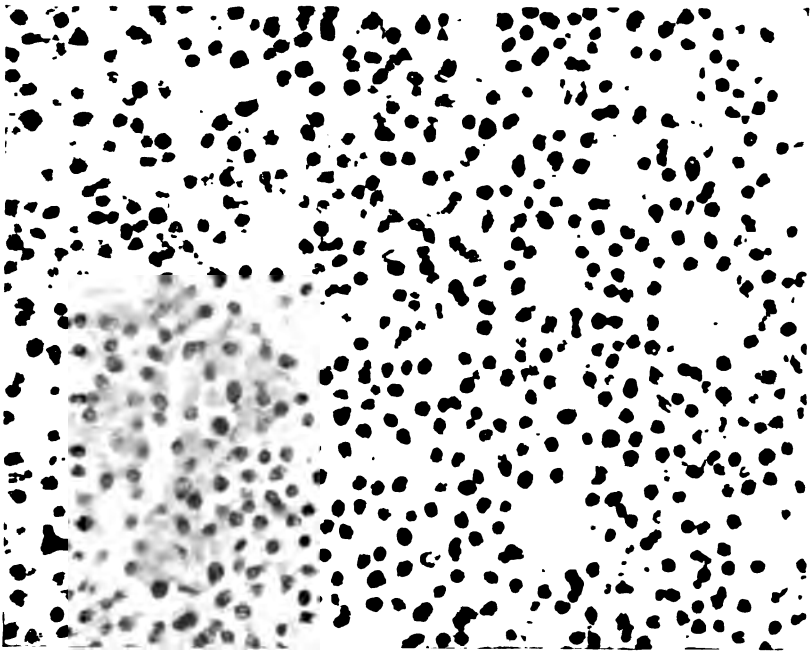

Fig. 7. Case VII.

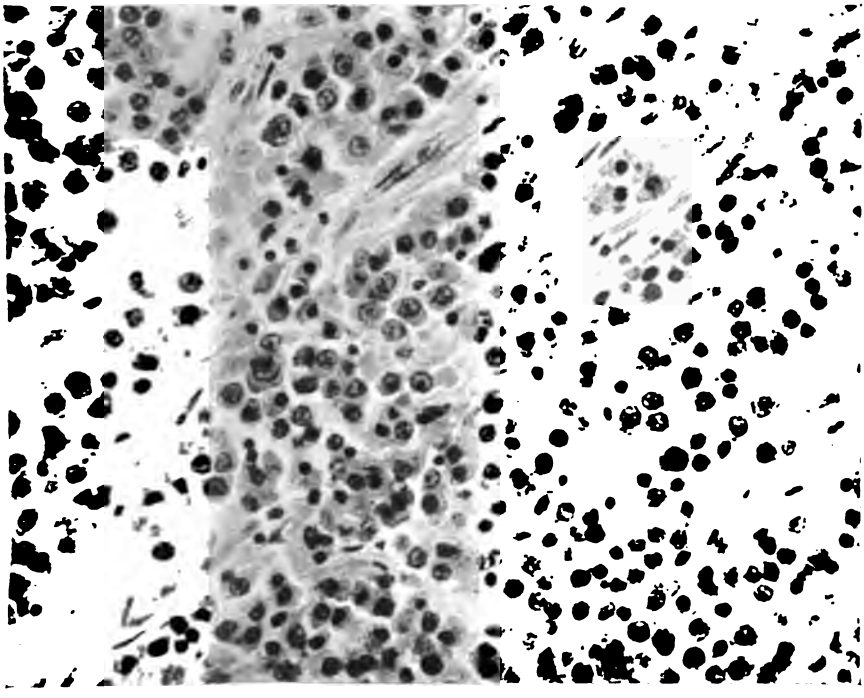

Fig. 8. Case VIII.

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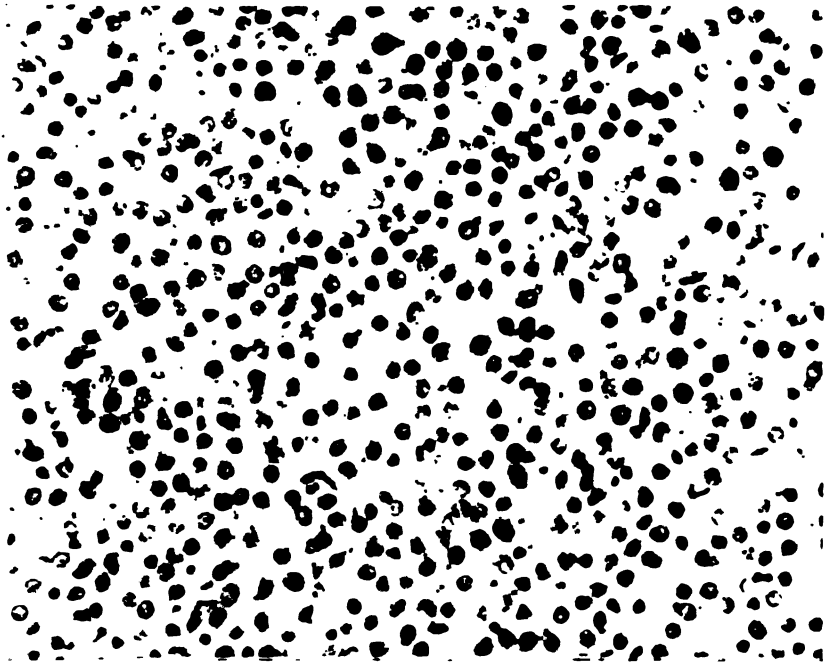

Fig. 9. Case IX.

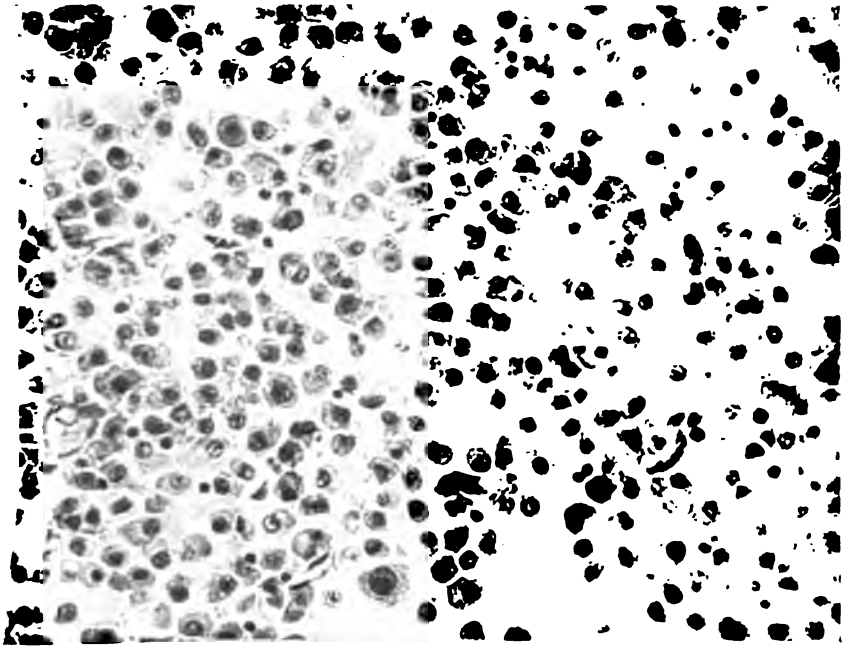

Fig. 10. Case X.

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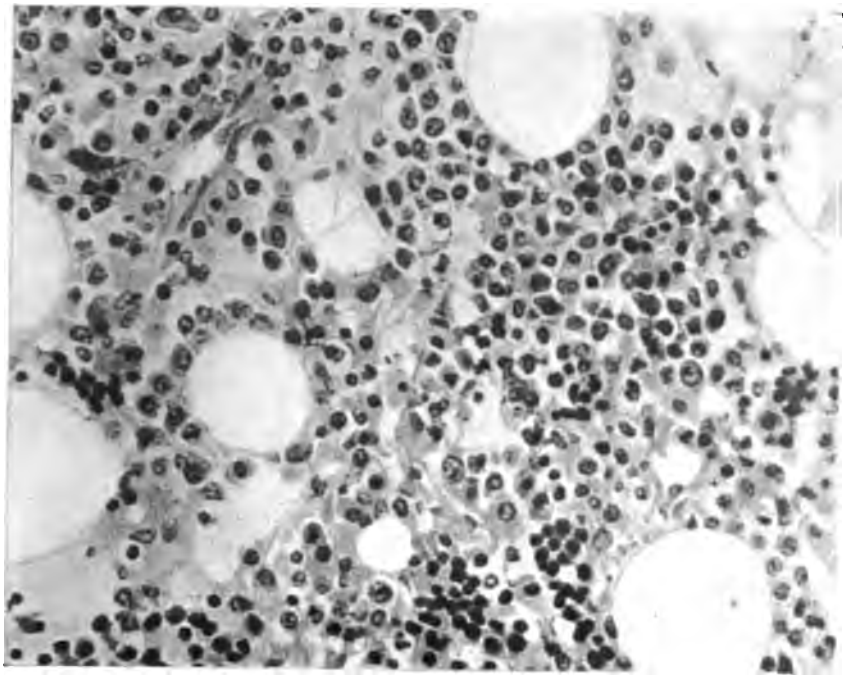

FIG. 11. CASE XI

FIG. 12. CASE III.

FIG. 13. CASE I.

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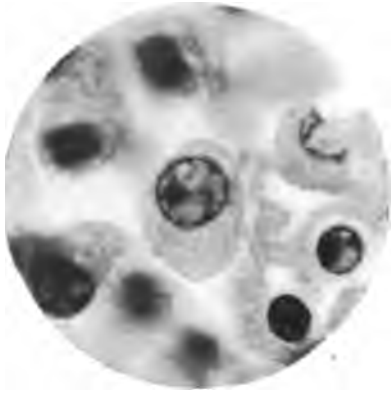

FIG. 14. CASE VIII.

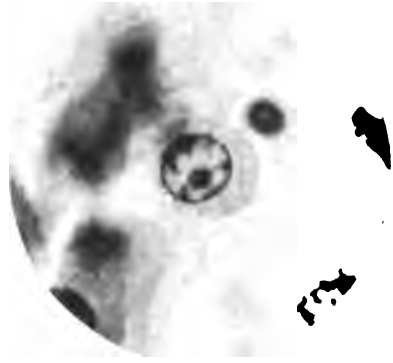

FIG. 15. CASE VIII.

FIG. 16. CASE V.

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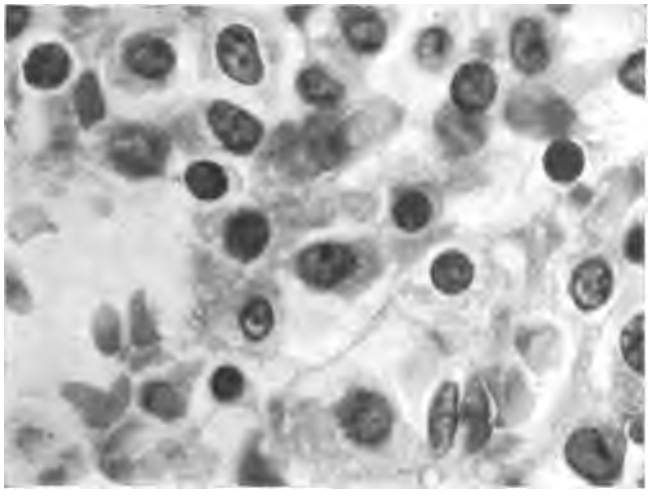

FIG. 17. CASE XI.

FIG. 18. CASE II.

FIG. 19. CASE VII.

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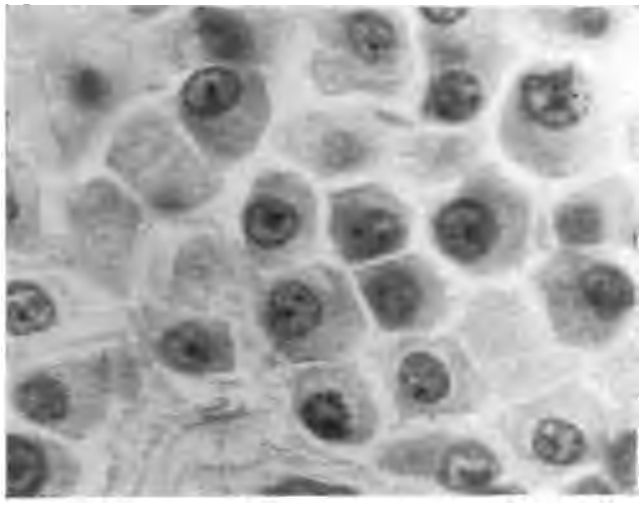

FIG. 20. CASE X.

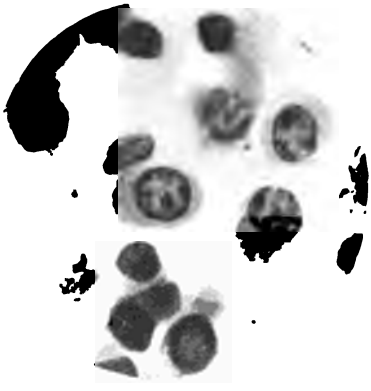

FIG. 21. CASE XI.

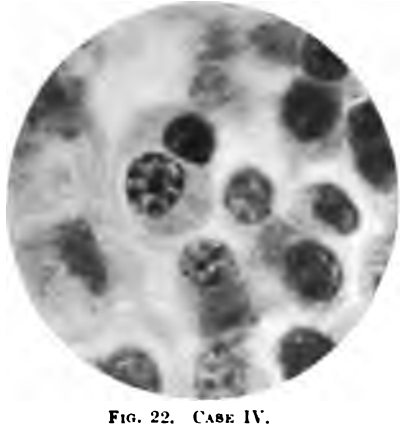

FIG. 22. CASE IV.

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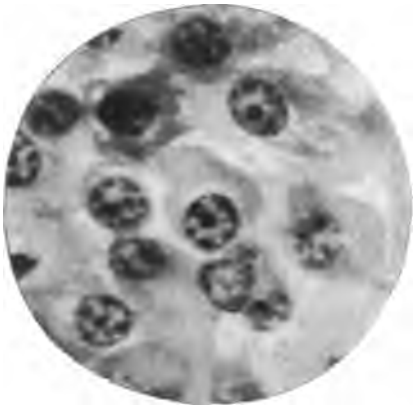

FIG. 23. CASE VI.

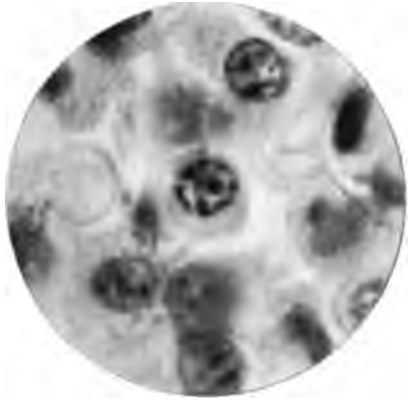

FIG. 24.

FIG. 25.

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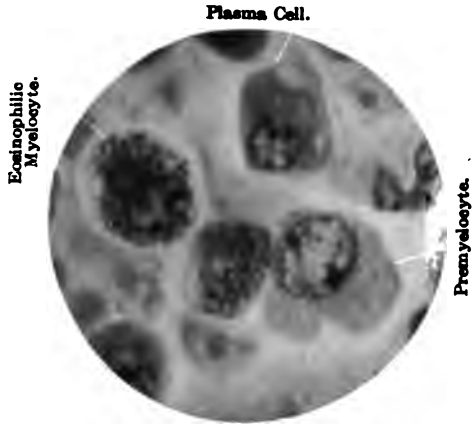

Fig. 26.

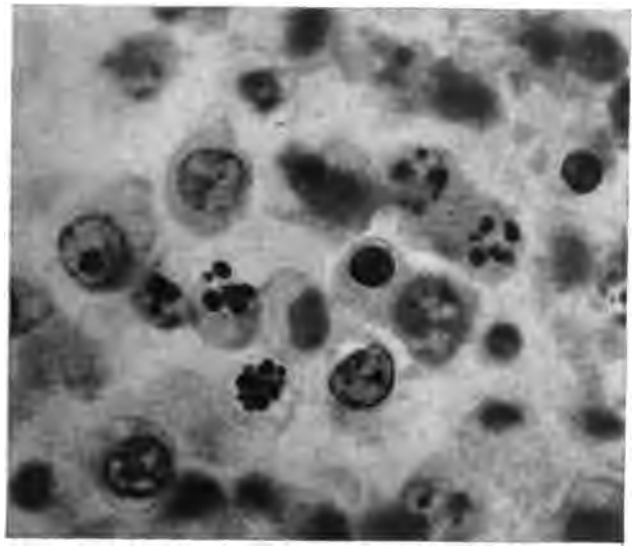

Fig. 27. Case VIII.

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other. Consequently, many of the cells show only a moderate rim of cytoplasm about the nucleus, and in such cells very marked eccentricity of position cannot take place. The typical nucleus is vesicular, with a distinct nuclear membrane, on which is clustered fine chromatin granules so as to give the nucleus a distinct, rather deeply staining, periphery, while scattered through the center there are rather few fine and occasionally coarser chromatin granules. (Fig. 21.) Quite a number of the nuclei show a distinct, rounded acidophilic, homogeneous body, the nucleolus. (Fig. 21.) These nuclei average 6.9 x 6.1 microns in diameter. Numerous cells are distinctly larger than these just described, and in them the nucleus is proportionately larger and has rather coarser chromatin granules without showing any other difference of structure. Some of these larger cells have two to five nuclei, though the multinuclear cells are not a predominating feature of the picture. Mitotic figures are easily found in cells of the types just described.

A common variation from cells just mentioned appears to arise from a gradual shrinkage of the nucleus, in which the nucleus as it shrinks becomes more compact and deeply staining, until it is finally represented by a shrunken, homogeneous, deeply staining mass. With the shrinkage of the nucleus there appears also to be a shrinkage of the cytoplasm, which also becomes denser and more homogeneous. The cells of the type just described very frequently show hemoglobin staining of their cytoplasm, and not infrequently they are as deeply stained with hemoglobin as are the red blood corpuscles. This phenomenon is observed most markedly in those areas in which there are scattered many free red blood corpuscles and in the vicinity of thin walled blood vessels and definite areas of hemor-

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rhage. Here and there a nucleus presents the appearance described in the preceding tumor, in which the nuclear material becomes aggregated into several small globules. These cells are not infrequently stained with hemoglobin and resemble closely the nuclei of certain megaloblasts in pernicious anemia, in which I have frequently noted similar changes in the chromatin.

Scattered between the cells in many areas of the tumor are many hyaline, slightly eosin staining or sometimes slightly basophilic, homogeneous droplets, which measure one to two microns in diameter. Here and there an eosinophilic leucocyte has been noted in the tumor, and also a few cells indistinguishable from the plasma cells of the connective tissue. In places there appear to be intermediate stages between cells identified as plasma cells and the tumor, and it is possible that these plasma cells have arisen from tumor cells which, after all, do not differ very markedly from plasma cells except that they are larger and the usual characteristics of plasma cells are less well marked. Probably the most striking thing in regard to this tumor, as in so many of the others, is the very uniform appearance presented by any field of the tumor and the slight variation in the appearance of the cells that predominate in the tumor, notwithstanding the variations in structure which have already been described.

Here and there are quite large phagocytic cells with included cells and cell fragments. The nucleus of these phagocytic cells, when it can be made out, is distinctly more vesicular and paler than the tumor cells, is apt to be elongated or irregular in contour and resembles the nucleus of the typical phagocytic endothelial type of cell. It is very probable that these cells are endothelial cells associated with the reticular framework of the

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tumor, as is so common in various forms of lymphosarcoma.

Sections stained with phosphotungstic acid hematoxylin show the cell characteristics already described, except that the cytoplasm after this treatment is rather more granular than when stained in other ways, and most of the cells show near the nucleus a paler zone in which is situated two small intensely black staining granules interpreted as centrosomes. Whereas it is common to make out two of these dots, not infrequently only one can be distinguished, while in other cells, especially in the cells which contain more than one nucleus, three or four dots can be made out.

CASE X (Myeloma " Y ").[1] The case has been reported by Dick (*Trans. Chicago Path. Soc.*, vol. vi, 1903-1906, p. 168), from which the following brief clinical note and autopsy findings were abstracted. The patient was a man thirty-two years of age,who, in July, 1902, had suddenly lost his sight in both eyes. Three days later he regained his sight in the left eye. Soon his eyes began to bulge and he was operated on twice for retro-ocular sarcoma. On Aug. 12, 1903, he had an epileptic seizure, followed by headache which lasted twenty-four hours. At this time there was a growth about the left orbit continuous with the frontal bone, and both eyes showed choked disks. Removal of the tumor was attempted, but the patient did not survive the operation more than a few hours.

On Aug. 15 an autopsy was performed by Dr. Wells. He found on the ninth rib at the angle a swelling just palpable externally, which measured 7 x 4 cm. This nodule lay beneath the pleura except where a button-like mass projected through the pleura. The skull

[1] This tissue was sent me by Dr. H. G. Wells, of the University of Chicago, to whom I wish to express my sincere thanks.

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showed a large operative defect in the frontal bone, 4 x 5 cm. At the outer angle of this there was a mass of tissue, 2 cm. in diameter, adherent to the bone, white and soft. More tumor tissue extended beneath the left zygomatic arch and was intimately connected with the bone. The bone was very soft and infiltrated with tumor. The entire left frontal lobe of the brain was occupied by tumor mass. No tumor metastases were found in the internal organs.

Stroma in this tumor is very slight in amount and is present only as fine connective tissue fibrils forming a reticulum in which lie tumor cells, at times closely packed together, at other times fairly well separated. (Fig. 10.) When closely packed, the cells are roughly polygonal in shape (Fig. 20); when loosely scattered, they are round or slightly oval. These cells average 12 x 9.7 microns in size. The cell outline is distinct, occasionally there is a suggestion of a cell membrane. The cytoplasm of many cells is finely vacuolated. Not infrequently these cells have a rather ragged, frayed-out border. In other sections many of the cells are very finely granular, almost homogeneous, and the vacuolated cells are less numerous. The cytoplasm in relation to the nucleus is quite abundant, and the nuclei almost always distinctly eccentrically placed in the cell. (Fig. 20.) The nuclei are round or slightly oval, with finely granular chromatin, often tending to group itself peripherally on the nuclear membrane. They measure 6.2 x 5.8 microns. Occasionally a cell shows a fairly distinct nucleolus. In many of the cells the nucleus shows shrinkage and has a more deeply uniformly staining nucleoplasm. A few cells show two or three nuclei. In some sections many of the nuclei show the chromatin collected in fairly coarse masses grouped peripherally on the nuclear membrane, and in

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places these chromatin masses appear to have become free in the cytoplasm, though still more or less closely grouped together, so that we have a cell in which at one point are several small chromatin masses grouped together without any definite arrangement and apparently not within a nuclear membrane. In most of the tissue repeated search failed to reveal any mitoses but in one section a single nucleus in mitosis was found and this cell appeared to be a tumor cell.

In a number of the cells the cytoplasm has a distinct yellowish tinge, suggestive of hemoglobin staining, but it cannot be definitely stated to be hemoglobin owing to the unsatisfactory way in which the tissue takes the stain. However, this condition is rather more marked in those portions of the tumor in which hemorrhage has taken place. In the sections stained with phosphotungstic acid hematoxylin the cytoplasm shows a quite distinct tendency to take the hematoxylin stain and is finely granular. Centrosomes could not be made out in some of the sections, possibly owing to unsatisfactory staining with phosphotungstic acid hematoxylin, but were quite distinct in a number of cells in one section.

CASE XI (St. Paul, Myeloma).[8] A man of fifty-eight, a patient of Dr. T. W. Stumm, St. Paul, Minn., began in August, 1905, to have a feeling of weakness in the legs, which at first came on after a hard day's work, but soon increased in severity so that he could scarcely walk. His legs were now stiff as well as weak, and there was slight pain starting in the small of the back and radiating down the legs. After two or three months the

[8] This tissue was sent me by Dr. T. W. Stumm, of St. Paul, accompanied by a clinical history of the case, from which I have abstracted the above notes. I desire to express my sincere thanks to him for this courtesy. The case will be published in detail later by Dr. Stumm.

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condition improved and he was able to do some work on the farm, but in the spring of 1906 the condition grew worse, and on Aug. 8 he entered the City and County Hospital in St. Paul. He could now walk around only a little by supporting himself by the bed or with a cane. He complains of pain in the small of his back, radiating down the thighs and legs, but when lying on his back rests very comfortably. Palpation with only very moderate pressure on the lower sides of the chests causes him to cry out with pain. This pain he locates in the dorsal region. When one taps along the vertebral column, he complains of pain in the lower dorsal region. He can only sit up by hanging his feet over the side of the bed and then holding on to the side of the bed with his hands. He holds himself pretty rigidly and moves slowly and cautiously in a spastic manner. Knee-jerks are much exaggerated and there is no ankle clonus. There were no very marked changes to be made out on physical examination other than these. He gradually became weaker, and for most of the time his temperature was one or two degrees above the normal. He died early in 1907.

Urine examined during his stay in the hospital showed no albumin and no special mention is made in the report of the presence or absence of albumose.

The tissue available for study from this case consists of several vertebræ preserved in formalin. Sections from these after decalcification show bone marrow and tumor quite intimately intermingled. (Fig. 11.) This fact renders it difficult in most places to positively separate tumor cells from cells which might be regarded as normal constituents of the bone marrow, and for this reason cell measurements were not made. However, there are foci here and there in which cells of quite uniform appearance are grouped together in the

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same relation to each other as is common in the other examples of myeloma, and it seems fair to regard these cells as undoubtedly the tumor cells and not normal constituents of the bone marrow. Most of these cells are irregular in shape, polygonal from pressure of adjacent cells. The cell outline is fairly distinct with no indication whatsoever of a cell membrane. (Fig. 17.) The cytoplasm is finely granular and of a less homogeneous ground-glass appearance than was the case with preceding tumors. The cytoplasm is possibly slightly basophilic, though the staining reactions are not perfectly satisfactory in this regard.

The nucleus in relation to cell body is rather large and there is some tendency to an eccentric position of the nucleus. The nuclei themselves are vesicular. There is a distinct nuclear membrane and fairly fine chromatin granules with some slight tendency to peripheral grouping. In some cells a fairly distinct nucleolus can be made out, but this is not common. Scattered among these cells are cells with slightly smaller, more deeply staining nuclei, which may be considered as tumor cells in varying stages of degeneration. There are also some cells in which the chromatin granules are coarser and definitely grouped on the nuclear membrane.

There is nothing particularly notable in those parts of the bone marrow in which no tumor cells occur. The bone marrow is moderately cellular, indicating a fair degree of proliferative activity, and megakaryocytes are quite numerous. Mitotic figures occur in association with tumor cells, but it is not possible to say with certainty that these mitotic figures are not in intermingled cells normal to the bone marrow. In general, the cells in this tumor correspond in appearance to the cells in the previously de-

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scribed tumors, but owing to their diffuse distribution in bone marrow in which a large variety of cells is normal, it does not seem fair to state that any transition between tumor cells and fairly typical plasma cells can be made out. The transition is suggested, but in a tumor of this structure error of interpretation can be easily made. However, it seems justifiable to include this tumor in the group and to consider it as a true myeloma, but it would not be possible to base very definite conclusions as to cell structure on a study of this case alone. That myelomata may sometimes grow diffusely in the bone marrow, as in this case, was well shown in Case I, in which the cells are relatively larger and more easily distinguishable from any cell of the normal bone marrow. In that case small groups of tumor cells could be easily recognized in the bone marrow of the femur, which macroscopically appeared perfectly normal, and entirely different in appearance from the other bones examined in which the marrow had practically been entirely replaced by tumor cells. In connection with the other tumors I think the cytology of this case can be understood and is properly to be interpreted as I have done above.

In my previous paper were collected from the literature those cases in which cell structure was described in detail sufficient to show the character of the cells composing the tumors. Those cases, in so far as may be judged from their descriptions, show a quite uniform cell type, though there are considerable minor variations in cells in the different tumors. For eight of the cases collected from the literature it is claimed by their reporters that the cells find a close analogy in the plasma cell.

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Of six it is believed that the cells bear a close relation to immature myelocytes. In one, the case of Sternberg, cytoplasmic granulation is described. In Ribbert's case an erythroblastic nature is claimed. In some cases no attempt to homologize the cells was made.

Since then several other cases have been reported. Permin (*Virch. Arch. für path. Anat.*, 1907, clxxxix, 439) describes three cases in which the cells measured 9, 8.5 and 8.5 microns respectively. It is evident from his descriptions and drawings that these tumors are essentially identical in structure. The cells he would group as premyelocytes. Hueter (*Münch. med. Wochenschr.*, 1907, liv, 811) reported one case briefly at a medical meeting. He described the tumor cells as round or polymorphous without granulations in the cytoplasm. He terms the tumor cells pseudomyelocytes. Charles and Sanguinetti (*Brit. Med. Jour.*, 1907, i, 196) give the following description of the cells in a typical case: The cells are of three types: round cells uniform in size with a large pale nucleus and large protoplasmic contents which is granular in character; round or polyhedral cells with a small, deeply staining nucleus and finely granular protoplasmic contents; large round cells with large, round, deeply staining nuclei and finely granular protoplasmic contents. They regard the tumor cells as resembling cells in the normal marrow which are the predecessors of myelocytes. Dévé (*Normandie med.*, Rouen, 1907, xxii, 289 and *Rev. méd. de Normandie*, Rouen,

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1907, viii, 207) has reported a case according to the title of his paper, but his paper was not available for verification. The question naturally arises, How far in the light of these cases can the histogenetic source of the tumor cells be determined?

A study of the bone marrow from a variety of cases shows that but two types of cell have any very close resemblance to the cells of these myelomata. Both are cells which have a slightly basophilic cytoplasm, distinct cell outline but no cell membrane. Both have a nucleus, frequently eccentric in position, with a distinct nuclear membrane and fairly constant nucleolus. In the one the nucleus is palely staining, with fine chromatin masses generally scattered throughout the nucleus, sometimes clumped more or less toward the center, but without any tendency to a mural arrangement. These cells (Fig. 26) belong to the myelocyte series, an early stage of development, usually before the specific granulation in the Ehrlich sense takes place, and are numerous in all active marrows. They may be called premyelocytes.

In the other cell (Figs. 24 and 25) the nucleus stains more deeply, the chromatin masses are coarser, there is rarely any central clumping of the chromatin masses. A nucleolus is a more constant feature. These cells appear to be constantly found in bone marrow. They are usually infrequent and never in large numbers. The maximum that I have ever found are scattered groups (Fig. 25, two cells in focus) of five

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or six cells with a few single cells, so that about every other field of a Zeiss 2 mm. objective and 4 ocular would show at least one of these cells. I have never been able to find any evidence of developmental changes in these cells. Their nature is not certain. They seem to have no relation to the formation of erythrocytes or polynuclear leucocytes. Of their relation to the lymphocyte series I can give no positive evidence. They appear closely related. Their closest analogue outside of the bone marrow is the plasma cell from which they differ in being slightly larger both cell body and nucleus, in having a less homogeneous ground-glass cytoplasm, in being rather less basophilic, in having not quite so coarse chromatin granules; but all these differences are of minor degree and do not serve to distinguish sharply these cells from the plasma cells of inflammatory tissue. However, as there are slight differences, I prefer to speak of these cells in the bone marrow as bone marrow plasma cells, and regard them as in some way related to the lymphocyte series of cells.

Which of these cells stands closest to the myeloma cell? As is evident from the description of the cells in the myelomata reported by me and by others, there is considerable minor variation in the cell picture. The features most constant in the tumor cells are cytoplasm finely granular or slightly vacuolated, slightly basophilic; a nucleus eccentric in position, with a tendency to a mural arrangement of chromatin and a nucleolus; the

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presence of centrosomes. There is some variation in cell size, the average of measurements in [9] each case being: [See table on opposite page.]

To compare with these I have made measurements of a number of cells in the bone marrow. The average of these is:

For myelocytes and premyelocytes from different cases:

11.5 x 9.25 microns;	nucleus,	8.0 x 7.5 microns.	
11.8 x 8.25	,,	,,	7.2 x 6.5 ,,
12.25 x 9.7	,,	,,	8.5 x 7.2 ,,

For bone marrow plasma cells from different cases:

9.7 x 7.0 microns;	nucleus,	5.1 x 4.6 microns.	
8.6 x 6.6	,,	,,	5.3 x 5.0 ,,
9.9 x 7.5	,,	,,	5.6 x 4.8 ,,

From these measurements it is evident that the cell body and nucleus of the myelocytes are rather larger than those of the tumor cells. The bone marrow plasma cells agree in size with the cells of those tumors which have the smaller sized cells. cases seem to me to present more similarity to the A glance at the cell descriptions in these will show that these tumors have cells which agree closely in structure with the bone marrow plasma cells. The other tumors have cells which, while retaining the characteristics in part of the plasma cells, yet show differences. Still these differences, though in the direction of the premyelocyte, do not often give a cell so large as the premyelocyte, and when compared side by side the cells appear to be more

[9] All these measurements were made on cells in tissue hardened in Zenker's fluid, embedded in paraffin and stained with eosin and methylene blue, except cases VII, VIII. The same lenses and micrometer were used throughout.

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Case VI,	cell body,	8.4 x	4.2	microns;	nucleus,	4.2 x	4.1	microns.
Case IV, sternal part,	,,	8.5 x	5.5	,,	,,	5.7 x	5.4	,,
Case VII,	,,	9.0 x	7.7	,,	,,	5.3 x	4.6	,,
Case IV, orbital part,	,,	9.4 x	7.6	,,	,,			
Case V,	,,	9.9 x	6.4	,,	,,	6.9 x	5.0	,,
Case IX,	,,	10.2 x	8.7	,,	,,	6.9 x	6.1	,,
Case II,	,,	10.4 x	6.8	,,	,,	6.0 x	6.0	,,
Case III,	,,	10.5 x	6.8	,,	,,	7.2 x	6.4	,,
Case VIII,	,,	11.2 x	10.0	,,	,,	6.6 x	6.1	,,
Case I,	,,	11.4 x	7.7	,,	,,	8.1 x	7.2	,,
Case X,	,,	12.0 x	9.7	,,	,,	6.2 x	5.8	,,

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closely homologous with the bone marrow plasma cells than with the premyelocytes. This is certainly true also for the cells in many of the tumors reported by others.

In other words it seems possible to arrange the cells of these tumors in series so that between the cells of succeeding cases the differences are slight, though the differences between the cells at the extremes are fairly great. This is well shown by comparing in series the photographs, Figs. 12 to 23. The cells of one tumor described by me are almost identical in structure with plasma cells of the marrow, and those in four others are but very slightly different. The cells in the other cases seem to me to present more similarity to the plasma cell than to the myelocyte. If the myelocyte is assumed to be the ancestral cell the departure from the type is very much greater. (Compare the premyelocyte in Fig. 26 with cells in the series given above.) It is probably not possible to give any convincing proof of the ancestry of these cells. The cases studied side by side and in comparison with bone marrow cells leave the impression that we have in these tumors a development from certain bone marrow cells, which I have considered to be bone marrow plasma cells. Whether this is true for all reported cases is exceedingly difficult to say, especially for those cases in which the cells are not described in much detail. Possibly some cases, as that of Sternberg, in which neutrophilic granules are described, may have to be regarded as an exception.

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In addition to this histological evidence as to the nature of the cells in myelomata the following observations may be considered in favor of their plasma cell nature though it is not claimed that they are conclusive. Eduard Müller (*Deut. Arch. für klin. Med.*, 1907, xci, 291) has described a simple method of testing the proteolytic leucocytic ferment by means of blood serum plates at a temperature of 55° to 60° Centigrade, thus inhibiting the growth of bacteria. Under these conditions leucocytes digest the blood serum, producing a depression where they come in contact with the serum. This ferment action, it has been already pointed out is not destroyed by the preservation of the cells in formaldehyde. At my suggestion Dr. Channing Frothingham, Jr., has tested in this way portions of tissue from cases I and VIII which had been preserved in alcohol. As a control bone marrow from a case of myelogenous leukemia similarly preserved in alcohol for a longer time was tested. With the tumor tissue no digestion of the blood serum took place while with the myelogenous leukemia bone marrow definite digestion resulted. Were the tumor cells histogenetically related to myelocytes, it might be supposed that they would cause digestion of the serum. This evidence for a myelocyte origin of the tumor cells is, to say the least, lacking.

Ribbert's (*Centralbl. für allg. Path.*, 1904, xv, 337) contention that the case studied by him was composed of erythroblastic cells is not supported by these cases. The frequent presence in my

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cases of cells stained with hemoglobin and resembling nucleated red blood corpuscles, as already described, suggests the possibility that a similar condition may have been present in Ribbert's case. In my cases it seems very certain that these cells result from a combination of cell degeneration and hemoglobin staining. Such hemoglobin staining of plasma cells is by no means uncommon, especially in the spleen where I have observed it many times, and this fact may be taken as some slight further evidence of the plasma cell nature of the tumor cells.

Certain nuclear changes regarded as degenerative phenomena are of frequent occurrence in these myelomata. Almost all show nuclei in varying stages of shrinkage. As the nuclei shrink, they stain more diffusely and more deeply until finally all evidence of intranuclear structure is lost. More interesting are the nuclear pictures shown in cases II, VIII, IX and X, in which there are many nuclei in which a process of nuclear segmentation has taken place, which results in the formation of a varying number of spherical chromatin masses of varying size and homogeneous structure. With both of these changes, as already pointed out, hemoglobin frequently is present in the cytoplasm.

In descriptions of myelomata the absence of mitotic figures has been quite often noted, and it has been suggested that the cells divide only by direct division. However, in my cases typical mitoses were found in cases II, III, IV, V, VIII,

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IX, X and XI(?), [10] and were quite numerous in some of these. Their absence in other cases is to be explained, I think, by the slow development of many of these tumors rather than by any peculiarity of the tumor cells. This theory is further supported by Case IV, in the sternal portion of which mitoses were easily found, while they were excessively rare or absent in sections from the orbital portion.

There is nothing in these tumors to suggest any transformation of cells along the line of development from premyelocyte to polymorphonuclear leucocyte. Sternberg is the only observer who has succeeded in demonstrating neutrophile granules in the cells of a myeloma. This fact in this single case does not seem sufficient evidence on which to base the opinion that all myeloma cells are myelocytes in some stage of development when we consider the great similarity of the cells in very many cases to plasma cells. If more cases like Sternberg's are accumulated, it would justify a subdivision of myelomata into (*a*) those with cells resembling plasma cells, and (*b*) those with cells resembling myelocytes. Even then it would still be possible without claiming a histogenetic relation between plasma cell and myelocyte to form a tumor group, having the main characteristics already described for the myelomata, in which all cases could be arranged in series with a tumor composed of cells identical

[10] In Case X only one mitotic figure could be found. In Case XI there is the possibility that the cells found in mitosis were not tumor cells but marrow cells.

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with plasma cells at one end of the series, and a tumor with cells identical with myelocytes at the other, while between would come cases whose cells represented a gradual transition from one to the other. Such a group would contain tumors showing no greater differences than occur within all other tumor groups, such as sarcomata, carcinomata, etc. However, with regard to the tumors actually studied by me, all would be grouped at the plasma cell end of such a series.

A study of these cases and a review of those reported in the literature strongly suggests that the myelomata are true tumors rather than the bone marrow manifestations of a systemic disease as claimed by Pappenheim (*Folia hematologica*, 1907, iv, Supplement Heft 2, 215) and that they belong to that general group of tumors which tend to extend or metastasize chiefly in a single system of the body. A common example of this tumor group are the lymphosarcomata or lymphocytomata. However, metastasis into the viscera does take place in some of the cases of myeloma, and many show a distinct invasive type of growth where they break through their bony bounds and infiltrate adjacent tissue. This in itself seems sufficient evidence for regarding the myelomata as tumors in the commonly used sense of that word.

SUMMARY.

A histological study of eleven cases of myeloma shows a striking similarity of cell structure with differences of minor degree. The common char-

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acteristics of the cells are a finely granular, slightly basophilic cytoplasm, an eccentrically placed nucleus, a nucleolus, centrosomes, a nuclear membrane and a tendency to mural arrangement of the chromatin. Certain nuclear changes, regarded as the results of degeneration are commonly found. Mitotic figures occur in most of the cases studied by me, though absent in a few.

Myelomata are to be classed with the tumors. They tend to remain localized in the bone marrow but almost all show evidence of invasive growth into adjacent structures, and in a few metastasis has taken place. These tumors then are malignant in the usual sense of the word, but their malignant properties are apt to appear relatively late in many cases.

With these characteristics there is a greater resemblance of the tumor cells to bone marrow plasma cells than to myelocytes. In most of the cases reported by other observers the cells show these characteristics and these tumors from a group within which the cells of individual cases show no greater variation than occurs in other tumor groups.

DESCRIPTION OF PLATES.*

Figs. 1 to 11. Low power (425 diameters) fields from eleven cases to show cellular character and scant stroma of myelomata.

Figs. 12 to 23. Cells (1,500 diameters) from each tumor, arranged in series to show the slight variations in cell structure.

Fig.	12	from case	III
"	13	" "	I
"	14	" "	VIII
"	15	" "	VIII
"	16	" "	V
"	17	" "	XI

*These photographs were made by Mr. L. S. Brown, at the Massachusetts General Hospital, for whose careful work I wish to express my thanks.

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Fig. 18 from case II
" 19 " " VII
" 20 " " X
" 21 " " IX
" 22 " " IV
" 23 " " VI

Fig. 24. Bone marrow plasma cell (1,500 diameters) from a case of pernicious anemia.

Fig. 25. Group of bone marrow plasma cells (1,500 diameters) from a case of cirrhosis of the liver.

Fig. 26. Premyelocyte, plasma cell and eosinophilic myelocyte (1,500 diameters) from a case of cirrhosis of the liver.

Fig. 27. Cells showing nuclear changes (1,500 diameters). From Case VIII.

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the milk. The so-called ductless glands may suffer an impairment of their functions in typhoid just as do the digestive glands, and these ferments if present in the milk would be of assistance to the patient.

The foregoing considerations made it seem desirable to see if any beneficial effects followed the giving of human milk to typhoid fever patients. Certainly no ill effects could follow the use by an adult of a food which is known to be the most easily digested and assimilated by the human being at the age when its power of digestion and assimilation is at its lowest stage of development.

During November and December, 1907, seven patients at the Boston City Hospital were given human milk which had been collected under the supervision of the writer. Five of these cases were on the service of Dr. G. B. Shattuck, and two on that of Dr. J. L. Ames, to both of whom I am indebted for the privilege of reporting the cases. I am also greatly indebted to Dr. E. P. Joslin for much valuable assistance in the work.

The milk was collected by Mrs. A. M. Henderson, a trained nurse. After visiting a large number of nursing mothers living in the tenement house districts, a few were found who had a superabundance of milk. These mothers and their babies were all examined by me and found to be healthy before the milk was used. Precautions were taken to have the milk drawn in a cleanly

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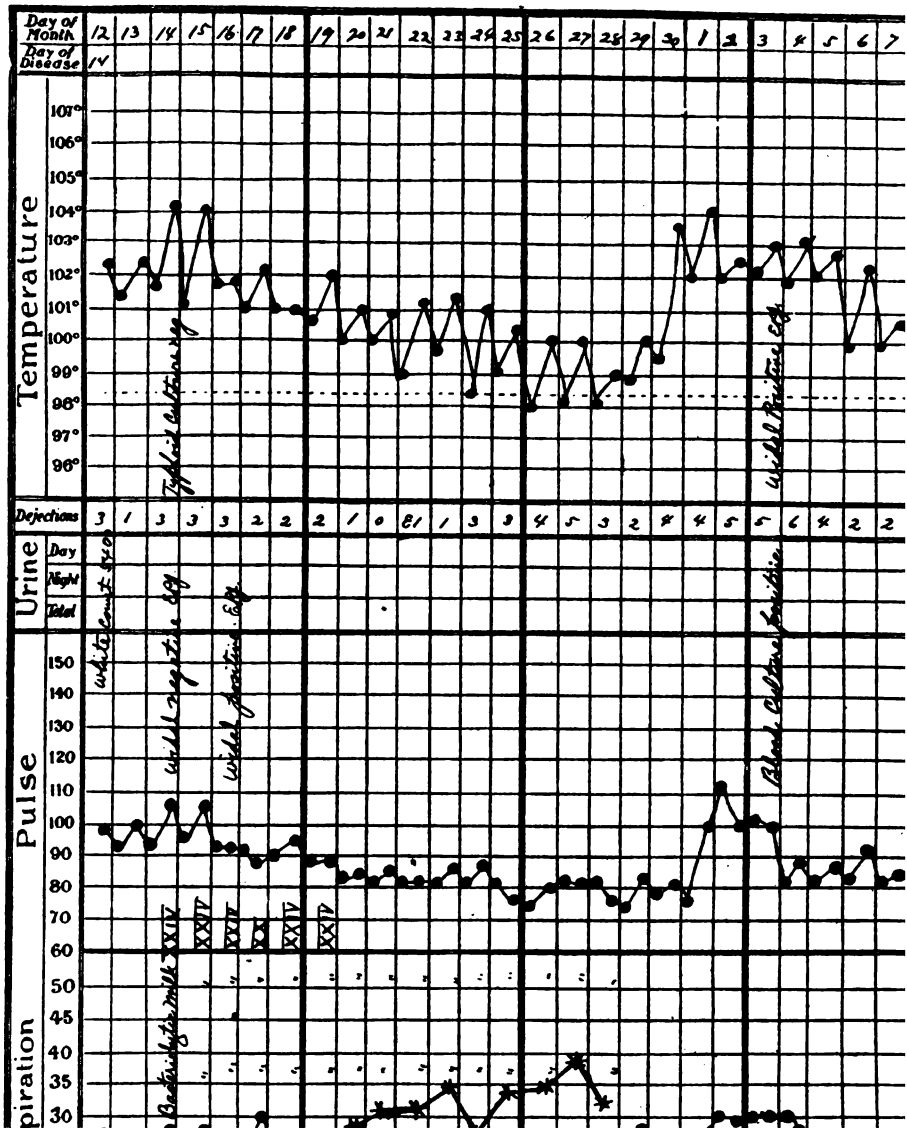

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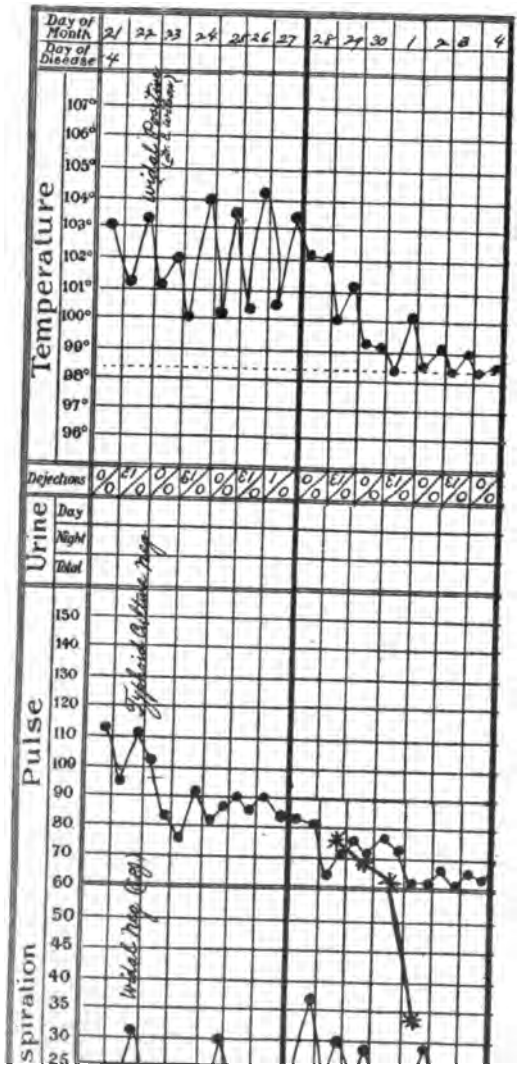

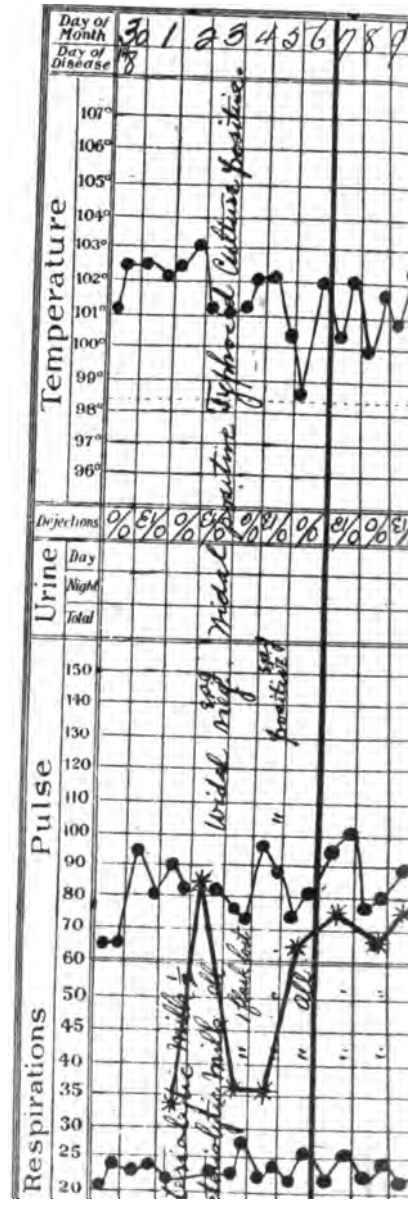

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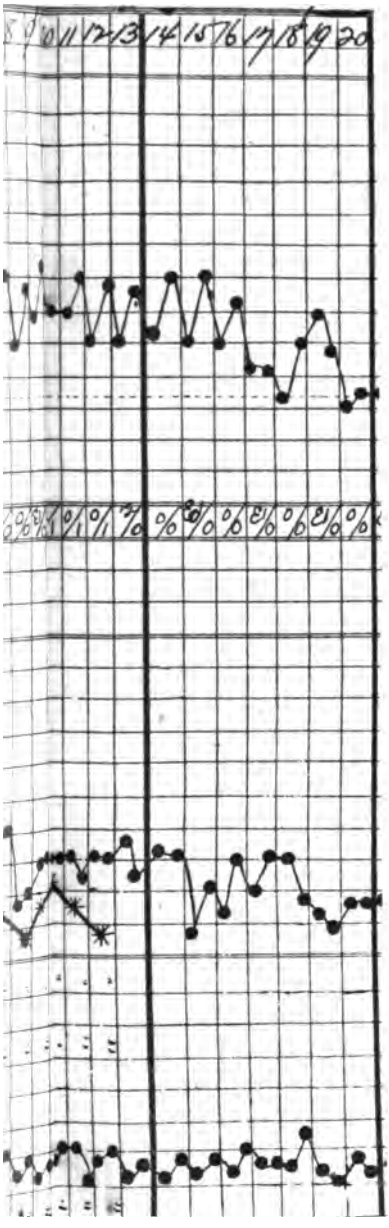

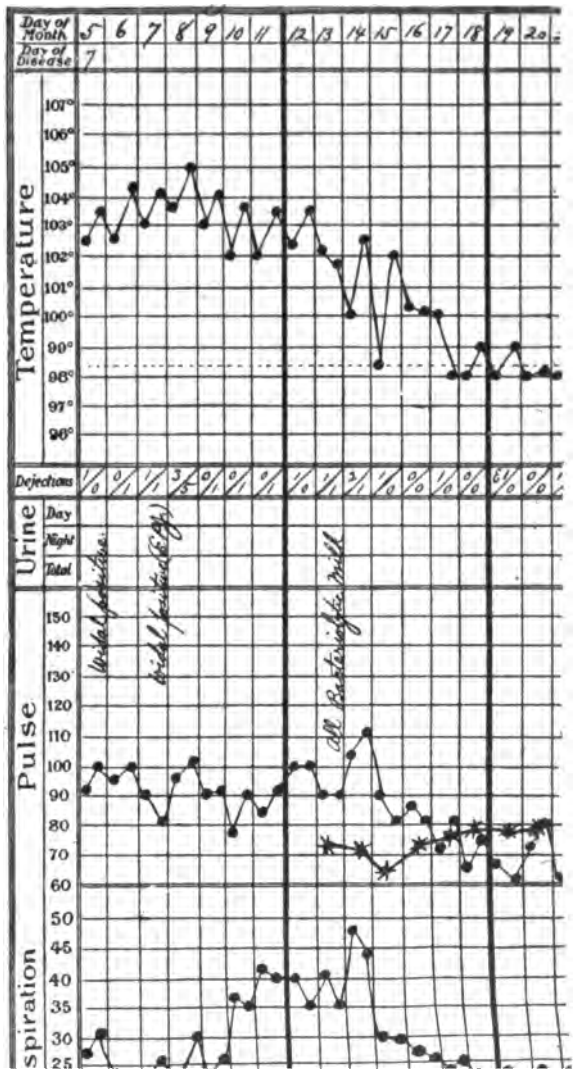

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diagnosis of bronchopneumonia being made only at autopsy. Although the bacteriologic examination showed a mixed infection, streptococci were especially predominant in all of these cases. I believe these cases represent a terminal infection not strictly to be classed as clinical bronchopneumonia. They occurred in children very sick with some other disease, were of sudden onset, great severity, brief duration, invariably fatal, and with slight or absent physical signs in the chest. To include them with the mixed infection group would, in view of their strikingly different and peculiar clinical manifestations, not give a fair picture of clinical bronchopneumonia, and I have therefore placed them in a separate class, which will be called the Terminal Infection Group.

Age.	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
2 yrs. or under,	100%	83%	28%	100%	60%
Over 2 yrs.,	0%	17%	72%	0%	40%

The only notable point in connection with the age is that in the influenza group the majority of cases occurred in children over two years of age while in the other three groups, the majority occurred in children under two years.

Origin. — All of the cases in the pneumococcus group were primary. Of the influenza cases, 3 followed whooping cough, the others being primary. Of the tubercular cases, 2 followed lobar pneumonia, the others showing no direct relation to any preceding disease. The majority of the cases of the mixed infection group appeared to be

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secondary to some infection of the upper air passages, such as an ordinary cold, with gradual extension downward into bronchitis, and finally to bronchopneumonia. A certain number of them followed one of the recognized contagious diseases, such as whooping cough or measles, but the small number of such cases does not indicate that this is not a very common origin of bronchopneumonia, because such diseases are not admitted to the hospitals.

Onset.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Gradual,	75%	59%	66%	0%	0%
Sudden,	25%	41%	33%	100%	100%

The percentage figures are not of very great significance as they are based on too small a number of cases, though they give a certain indication of difference in clinical type. The notable point is that in the pneumococcus group the onset was invariably sudden, whereas in the other three groups it was usually gradual. In two of the tubercular cases, classed as having a sudden onset, the disease began with typical lobar pneumonia, which was followed later by the finding of tubercular bronchopneumonia at autopsy.

General condition.

	Mixed.	Tubercular.	Influenza.	Pneumococcus.	Terminal.
Good,	17%	75%	57%	40%	0%
Poor,	83%	25%	43%	60%	100%

The figures represent the general condition when the patient was first seen. In the fatal cases it grew progressively worse. The notable

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	Age.	Onset.	Mental condition.	Temperature.	Duration.	Termination.	Signs in chest.	Sputum at at autopsy.
Mixed	Infants	Gradual	Affected	Moderate	Medium	Death or lysis	Diffuse	Mixed Infec.
Tuber.	,,	,,	Clear	,,	Long	Death	Localized	Tuber. Bac.
Influenza	Children	,,	,,	,,	Very long	Lysis	Shifting	Infl. Bac.
Pneumococcus	Infants	Sudden	Affected	High	Short	Crisis	Localized	Pneumococcus
Terminal	All ages	,,	,,	,,	Very short	Death	Diffuse or none	Mixed-Streptococci ?

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with a tendency to marked remissions, which usually occur in the morning, but which may occur in the evening, the chart often showing a very characteristic up-and-down curve. The duration is long, about two to six weeks, or even more. The prognosis is very bad. None of the cases in this series recovered, two being discharged not relieved. I believe, however, from cases which I have seen but have not been able to prove tubercular, that recovery is possible. The most characteristic physical sign in the chest is the gradual appearance of rather large areas of consolidation which persist for a long time. The areas may be small, and there may be diffuse crackling râles generally distributed, so that the physical signs may be exactly the same as those seen in the common bronchopneumonias of the preceding type. Tubercle bacilli are often difficult to find in the sputum. At autopsy is found the characteristic caseous pneumonia.

This form of bronchopneumonia is to be distinguished from the common mixed infection form, by the clear mental condition of the patient, by the tendency toward localized large and persistent areas of consolidation in the chest, and more than all by the peculiarities of its temperature curve. Nevertheless, it is often very difficult to make the diagnosis, particularly when the temperature curve is not characteristic, and when the signs in the chest are diffuse.

3. *Influenza bronchopneumonia,* which is not common, except when influenza is generally prev-

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alent. It is a disease principally of childhood and adult life rather than of infancy. It usually follows an influenzal infection of the higher air passages, which finally involves the lungs. The onset may be sudden in the first place, but the symptoms of pneumonia usually come on gradually. The general condition is often serious at the start, but may be good. The nervous system, in children at least, is usually but little affected. The temperature is irregular, for the most part moderate, but with a tendency toward high exacerbations which last from a few hours to several days. Fever is very prolonged, the temperature returning very gradually to the normal. The entire duration of the illness is strikingly long, about 2 to 8 weeks. The prognosis is good, complete recovery being the usual termination. The signs in the chest commonly do not involve all parts of the lungs at once, and diffuse crackling râles are not found. Recognizable areas of consolidation occur successively in various parts of both lungs, persisting only for a few days, and then disappearing, leaving in their place a collection of râles. This shifting appears to be quite characteristic, and can best be understood from the illustrative case given below. Influenza bacilli, both within and without the leucocytes, are found in great numbers in the sputum, which is very purulent in character. I have seen no autopsies of this type.

This form of bronchopneumonia is to be distinguished from the common secondary form by

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its occurrence later in life, by its generally less serious nature, by the less common affection of the nervous system, by its prolonged duration, and more than all by the peculiarities of the physical signs found in the chest. It is to be distinguished from the tubercular form by the differences in the temperature curves, by the tendency to become progressively better, and by the shifting character of the signs in the chest.

4. *Primary pneumococcus bronchopneumonia.* — This is essentially a disease of the first two years of life. Both its clinical aspect and the findings in the sputum suggest that it is caused by an infection of the pneumococcus only. Like lobar pneumonia, it occurs in well patients, and the onset is sudden. The nervous system is usually affected to some extent, as in lobar pneumonia. The temperature rises rapidly, is high and steadily maintained, and falls by an abrupt crisis. The duration is short, resembling lobar pneumonia. The prognosis is much more favorable than in the common secondary bronchopneumonias. Convalescence is rapid. The physical signs in the chest are diffuse, consisting of crackling râles, with or without small areas of consolidation, and exactly resembling the signs found in the mixed infection type. The sputum resembles that of lobar pneumonia, being tenacious, not purulent, and containing few organisms except the pneumococci, which are found both within and without the leucocytes. At autopsy the lesions resemble those of the common secondary type.

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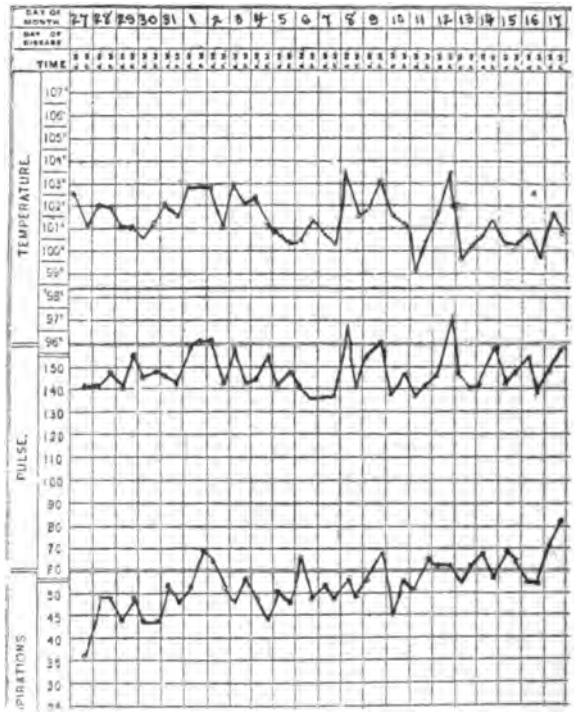

CHART I. MIXED INFECTION.

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THE DIAGNOSIS OF CIRCULATORY CONDITIONS BY TEMPERATURE MEASUREMENTS.

BY THEODORE JEWETT BASTMAN, M.D., BOSTON,
Medical House Pupil, Massachusetts General Hospital, 1907.

ATTENTION has long been paid by physiologists to measurements of the temperature of the skin in various parts of the body under varying degrees of warmth of the surrounding air; and the effect of exercise on the superficial temperature has been studied, particularly by Kunkel.[1] No observations, however, so far as I can find, have been published regarding the relation of body temperature to that of the extremities in disease.

This question was suggested to me by Privat Docent Dr. Ludwig Braun, of Vienna, to whom I take this opportunity of expressing my gratitude for his constant aid and suggestion during the course of my investigation. I wish also to express my thanks to Primarius Dr. Ritter von Frisch, through whose kindness I was enabled to carry on the work in his Abteilung in the K. K. Allgemeines Krankenhaus, in Vienna, and to his assistant, Dr. Hawdek, for many kindnesses.

When we measure the temperature of the skin in different parts of our extremities, we find that the nearer to the heart we measure, the higher the temperature. Davy,[2] using a mercury ther-

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mometer, found that, with a room temperature of 20° C.,* the temperature of the sole of the foot was 32.2° over the rectus femoris, 32.78°, and in the inguinal fold, 35.84°; and Kunkel,[3] using the more accurate thermo-electric measurement apparatus, found at the same room temperature the following values: dorsum of hand, 32.5° to 33.2°, forearm 33.7°, upper arm 34.3°, calf of leg 33.6°, thigh 34.2°.

The temperature of a part is dependent upon its chemical heat production, and upon the quantity of blood flowing through the part in a unit of time; that is, upon the rate of flow of the blood. Since the chemical heat production in the extremities in a state of muscle-rest is of extremely slight importance, the above mentioned differences in temperature can be caused only by the cooling which the blood undergoes on its way from the heart to the periphery. The farther a part is from the axis of the body, the lower its temperature.

It is, from the physiological point of view, of great interest that from the temperature of the skin surface we can judge of the circulation in the underlying tissues, although, as we shall see later, in varying degree in different parts of the body. In this regard, Tigerstedt[4] says: "The metabolism of the skin is slight, and the warmth of the skin is therefore derived principally from the heat radiated to it directly, particularly from the blood flowing in the deeper vessels. The greater the

*Throughout this article the temperature used is Centigrade.

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quantity of this blood. the warmer the skin. During its circulation through the cutaneous vessels, the blood is cooled, and the quantity of heat radiated to the surrounding tissues must be in direct proportion to the amount of blood supplied."

Klapp [5] has shown that hyperemia artificially produced on the surface of the body extended even to the viscera, and from this we must assume the presence of hyperemia in the deep portions of a limb when we find an increase in its surface temperature,[6] and Bier [7] shows that even a moderate degree of passive congestion is not confined to the skin, but extends even into the bone-marrow, and says further: "In deep-lying inflammatory processes the skin contains much more blood than it normally does; such is the case even with the skin of the abdominal wall in deep inflammations."

O. Müller [8] found that cold diminishes the volume of the forearm, heat slowly increases it, and also causes it slowly to diminish.

Finally, we find the same idea in an article by Exner [9] who says: "For the understanding of the phenomenon of erection, it is important to note the very striking increase of temperature of the penis. Wherever we observe in the body of a warm-blooded animal such a rise in temperature, it means, in the first place, an increase in the amount of blood which enters the organ in a unit of time. There is no reason to believe — indeed, under the existing anatomical relations it is very

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(8) It furnishes us with a method of distinguishing the edema arising from passive congestion from that due to nephritis.

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ON THE TRANSLATION OF CLINICAL DESCRIPTIVE TERMS INTO THEIR HISTOLOGICAL EQUIVALENTS IN DISEASES OF THE NOSE AND THROAT.

BY J. L. GOODALE, M.D., BOSTON,

Medical House Pupil, Massachusetts General Hospital, 1888; Assistant in Laryngology, Harvard University; Assistant Physician for Diseases of the Nose and Throat, Massachusetts General Hospital.

THE mucous membrane of the upper air passages offers peculiar advantages for study, since within certain limits clinical deviations from the normal may be brought into direct correspondence with their histological phenomena. It is advantageous for the student to learn to associate the macroscopic with the microscopic appearances, as this practice not only gives added interest to his examination, but is of very direct value in the recognition and interpretation of the slighter departures from the normal.

The object of the following paper is to present a working scheme for the student, by aid of which he will be enabled to carry more readily in his mind this translation of terms. In such a scheme it would be found advantageous to omit consideration of new growths, since for obvious reasons, where such alterations are present, the most direct method is to excise a portion of the tissue, and examine it histologically. Such conditions as tuberculosis and syphilis are also omitted.

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In the larger proportion, however, of diseases of the upper air passages, recourse to microscopic examination is not justifiable. If the student has clearly fixed in his mind the definite relation of clinical deviations from the normal with the histological changes, he will be enabled, on inspection, to approximate within narrow limits the more direct results of histological study. Inasmuch as the majority of the alterations which come under the observation of the laryngologist are superficial and displayed in the mucous membrane, a direct translation of clinical into histological terms would appear frequently possible. Where the alterations are more deeply seated, such a translation may be obtainable chiefly by inference.

The practical application of his method demands a clear knowledge of normal histology. The student should have readily available in his mind the salient features of the normal structure which he is inspecting. With this requirement presupposed, we may proceed to consider the scheme for study which it is proposed to offer. For convenience, we shall make the following division of the subject:

1. The visual details of the nose and throat.

2. The deeper structures invisible to the eye by reflected light.

1. The visual image of a given surface in the nose and throat is formed by the association of the structural units of the part. With an opaque surface, the image will be flat and in one plane, or

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it may possess relative depth, dependent upon the degree of penetration of light rays below the surface.

The elements of the visual image are color, including translucence, shape or physical character of the surface, and presence of extraneous material which may be fluid, cellular or amorphous solid.

The color depends both upon the number, size and degree of distention of the blood vessels, and upon the ratio existing between the interstitial fluid and component cells. The translucence of the part depends upon the structure of the epithelium, and upon the amount of interstitial fluid near the surface. The shape or physical character of the surface depends upon the type and condition of the epithelial structures.

2. The deeper structures, invisible to the eye by reflected light, manifest their alterations by changes in shape, size and consistence. The shape depends upon the disposition of the subepithelial elements. The size is determined by the quantity of the various component units of the structure, both fluid and cellular. Consistence, recognized by probing, varies both in proportion to the quantitative ratio existing between the fluid and cellular elements, and according to the relative disposition of these to each other. The association of these different units in a definite fashion gives rise to the normal clinical picture, and by their variation are produced the various pathological alterations.

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For purposes of space we shall restrict our examination in the present paper to the nose and faucial region.

THE NOSE.

Let us now take up some of the more common alterations of the nose and endeavor to interpret them histologically. We will consider, first, the normal histology of the tissue in question. Taking, for example, a section of the nasal tissues and examining it under the microscope, we find columnar ciliated epithelium, covering a thin mucous layer perforated by canaliculi through which there is a continual exosmosis of serous fluid to the surface. Below the mucous layer is a fibrous tissue of a varying degree of vascularity, containing mucous and serous glands, discharging their contents upon the epithelial surface. Between the fibrous tissue elements of this region is fluid in varying quantity, together with free cells, aggregated chiefly about the glands, and immediately below the mucous layer where it is disposed to form the lymphoid layer. We see thus that the normal appearances depend upon the association of a certain type of epithelium and of the mucous layer, upon the size, number and degree of distention of the blood vessels, upon the amount of interstitial fluid, the number and character of adventitious cells, and upon the character, degree of activity and number of the glands. Extraneous material is fluid and perceptible only as it lends a moist appearance to the surface.

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Passing now to pathological alterations of the visible tissues within the nose. we may proceed to enumerate the various factors in the order already given.

Color may be increased diffusely or locally. If diffusely, and associated with increase in size, we may infer distention of the blood vessels; if with diminution in size we may believe that less interstitial fluid is present or fewer cellular elements, the blood vessels, therefore, relatively preponderating. The first condition is found in acute rhinitis, the second in atrophic rhinitis. Local heightening of color would denote the existence of circumscribed irritation as from previous trauma.

Diminution of color may occur from general anemia, or as the result of contraction of the blood vessels or from a relative increase in the other tissue elements. In pallor from anemia we find normal translucence, indicating that there has has been no change in the tissue cells or in the amount of interstitial fluid. If the blood vessels are contracted, symmetrical diminution in size is found, as after the application of cocaine or adrenalin. In pallor, without changes in translucence, and with increased size, we should expect increase either in the amount of the interstitial tissue or in the number of the glands or of the cells of the lymphoid layer. The character and amount of the surface fluid will here throw light upon the condition of the glands. In adults with increased resistance to the probe, fibrous tissue hy-

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perplasia is probable, while in children with normal consistence of the part, we should expect increased infiltration in the lymphoid layer below the mucosa. In pallor with heightened translucence, we infer increase in the amount of interstitial fluid. If the amount of surface fluid is little or not at all increased, true edema is present without heightened exosmosis or glandular activity, as in nasal polypi. If the surface fluid is increased in quantity and thin or fails to coagulate on heating or treating with acid, we may infer widening of the canaliculi in the basement membrane and an increase in the interstitial fluid, as is found in vasomotor rhinitis. Such conditions may be either diffuse or local, and in the latter case their recognition may often be the chief clew to a correct diagnosis.

Loss of translucence of the epithelium, denoting disappearance of the columnar epithelium, occurs in various forms of atrophy, such as simple localized atrophy of the septal mucous membrane, in diffuse atrophy of ozena, and that occurring as the final result of syphilitic infiltrations. This loss of translucence is a factor of great importance in differentiating the atrophy of ozena from undeveloped turbinates, such as occurs in young women with associated arterial and uterine hypoplasia. In the latter case, the undeveloped turbinates give rise to the impression of atrophy, but inspection of their still translucent surface demonstrates the preservation of the columnar ciliated epithelium and excludes ozena.

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Period.	Date.	Vol.
	1906.	ccm.
I.	Nov. 7	3,470
	„ 8	2,300
	„ 9	2,300
	„ 10	2,080
	„ 11	1,940
	„ 12	1,940
	„ 13	1,940
II.	„ 14	1,970
	„ 15	1,680
	„ 16	2,050
	„ 17	2,110
	„ 18	1,930
III.	„ 20	2,220
	„ 21	2,200
	„ 22	1,980
IV.	„ 23	2,130
	„ 24	2,250
	„ 25	2,460
	„ 26	2,550
V.	„ 27	2,260
	„ 28	2,530
	„ 29	2,360
	„ 30	2,430
VI.	Dec. 1	2,360
	„ 2	2,340
	„ 3	2,340
	„ 4	2,500
VII.	„ 5	2,850
	„ 6	2,620
	„ 7	2,660
	„ 8	2,430
VIII.	„ 9	2,410
	„ 10	2,440
	„ 11	2,370
IX.	„ 12	2,400
	„ 13	2,380
	„ 14	2,670
	„ 15	2,300
	„ 17	2,400
	„ 18	2,820

*Twelve grams of sodium

In these observations

meal 88%. · Potato 90%.

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CHART I. CASE No. 94.

Nitrogen.	Ammonia.		Urine, total sugar.	Total carb. in diet.	Carbohydrate, balance.	Weight of Patient.	In addition to "A Strict Diet."				
	Total.*	Per cent of nitrogen.					Milk.	Oatmeal.	Cream.	Potato.	Oranges.
gm.	gm.		gm.	gm.	gm.	lb.	ccm.	gm.	ccm.	gm.	gm.
13.3	5.2	32.	190	60	—130	118	500	10	250	15	150
11.2	4.2	31	125	60	—65						
15.5	4.8	26	112	60	—50						
			104	60	—45						
10.5	3.9	31	89	60	—30	119	†				
9.5	3.5	31	97	60	—40						
9.1	3.5	32	94	60	—35						
			104	80	—25		250	30	500		300
10.0	3.2	26	77	80	+5(?)	120					
10.0	3.2	27	105	80	—25						
			113	70	—45						150
11.7	3.9	27	100	70	—30	122					
10.9	4.2	32	117	70	—45		250	30	500		300
			103	70	—35	124					
10.0	4.0	33	89	70	—20						
			107	70	—35		250	10	500		300
			104	70	—35						
11.0	4.4	33	103	70	—35	121					
			106	70	—35						
			80	55	—25			10	500		300
			68	55	—15						
10.8	4.6	28	94	55	—40						
11.1	4.7	35	95	55	—40						
			81	55	—25	117		25	250		300
			81	55	—25						
11.2	4.6	34	87	55	—30						
			89	55	—35						
11.7	5.2	37	84	64	—20	115		71	250		
			72	64	—10						
11.4	4.7	34	86	70	—15		120				
9.8	4.6	39	63	64	0(?)						
			60	40	—20	114		25	250		150
			67	40	—25						
8.8	3.6	34	67	40	—25					Rice	
10.2	3.5	29	62	60	—2			25	250	10	300
			78	60	—20						
			88	60	—30						
9.3	3.7	34	71	60	—10						
			73	60	—15						
			89	60	—30	117					

*carbonate were taken daily. † Milk changed to 250 ccm., and cream to 500 ccm

he carbohydrates in the food were reckoned as follows: *Milk 5%; Cream 4%; Oat-*

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both at its lowest (Period II) and highest (Period VII) levels when the carbohydrate balance was low. In other words, variations amounting to 25 gm. of carbohydrate in the diet of a severe case of diabetes with a minus carbohydrate balance of 20 to 40 gm. show no effect on the acidosis as measured in terms of ammonia. Further, it would appear that the restrictions of diet to 100 gm. carbohydrate, when a patient has been taking double that amount, is a perfectly safe procedure. The constancy of the amount of ammonia excreted on successive days is reassuring. This is notable in Period I and Period II, also in periods III, IV, V, VI, and again in periods VIII and IX. The large amount of ammonia in the oatmeal Period VIII is not what we should have expected.

The closeness with which the ammonia-nitrogen ratio follows the total ammonia is at once striking. On Nov. 9, the total ammonia was 4.8 gm., one of the highest limits reached in this case. Without a knowledge of the total nitrogen on that date, an erroneous impression of the severity of the case would have been gained. The great increase of total nitrogen, however, accounts for it, as the change in the ammonia is but little greater than would be expected with the increase of nitrogen. The ammonia-nitrogen ratio in this instance is probably a safer guide to the true acidosis than is the total ammonia. This would also seem apparent by a comparison of the total ammonia and the per cent of nitrogen in the form of ammonia on the following days:

Date.	Total ammonia grams.	Ammonia-nitrogen ratio.	Total nitrogen gram.
Nov. 9	4.8	26%	15.5
Dec. 5	5.2	37%	11.7
„ 7	4.7	34%	11.4
„ 8	4.6	39%	9.8

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Best

Date.	Vol.
1906	ccm.
Oct. 30	3,125
Nov. 14	3,500
Dec. 5	3,510
„ 6	3,285
„ 9	2,625 +
„ 11	2,400
„ 14	2,850
„ 18	2,370
„ 21	2,040
„ 23	2,340
„ 24	2,430
1907	
Jan. 10	3,000
April 21	2,750
Aug. 13	3,000
Oct. 21	3,250
Nov. 29	4,000
Dec. 16	4,500
„ 23	

Date.	Vol.	Di
1903	ccm.	
Spring	7,000	
1906		
Sept. 27	4,000	+
Oct 11	4,250	+
Nov. 6		+
Dec. 4		+
1907		
March 12	5,000	+
„ 14	4,000	+
„ 18	4,750	+
May 10	5,250	+
July 5	7,000	+
Nov. 27	5,750	
1908		
Jan. 26	3,720	
„ 27	3,940	
„ 28	3,210	
„ 29	3,210	
„ 30	3,190	
„ 31	4,600	
Feb. 1	4,050	
„ 2	3,610	
„ 3	360	
„ 4		

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CHART II. CASE No. 139.

eight 138; weight Oct. 13, 1906, 123¾; Dec. 16, 1907, 120¼.

Nitrogen.	Ammonia.		Urine, total sugar.	Total carb.	$NaHCO_3$	Carbohydrate balance.
	Total.	Per cent of nitrogen.				
gm.	gm.		gm.	gm.	gm.	gm.
24	4.2	15	198		12	
32	5.2	13	176		12	
20	5.8	23	129	70	12	—50
18	5.7	26			12	
16	4.8	26	109	63	12	—45
15	5.6	31	96		12	
16	6.1	31	95		12	
13	6.4	41	68		12	
11	5.3	41			12	
13	6.1	40	86		12	
10	4.7	40	97		12	
	6.1		138		12	
	5.7		86		12	
			108	44	12	—65
	4.8		120	62	12	—60
	7.3		128	68	12	—60
			90	50	12	—40
	Diabetic coma; death					

CHART III. CASE No. 135.

ætic id.	Acetone and diacetic acid.	Nitrogen.	Ammonia.		Urine; total sugar.	Total carbohydrates.	$NaHCO_3$	Weight of patient.
			Total.	Per cent of nitrogen.				
	gm.	gm.	gm.		gm.	gm.	gm.	lb.
					490			
+					188			127¼
+		25.0	3.2	11	173		20	128¾
+		23.9	2.7	11			16	130¼
+		22.8	3.2	12			12	132¾
+ +			6.8		192		12	
+ +			6.1		171		12	
+ +			6.9		246		12	
+			6.1		212		12	
+ +					386			121
					288			
	7.9	21.8	5.1	19		135	0	88¼
	7.8	19.6	5.2	22		135	0	89¼
	7.3	20.5	5.3	21		135	0	86¾
	7.3	19.2	5.0	21		135	0	85¾
	8.7	16.3	4.2	21		135	25	85
	12.6	19.1	5.2	23		120	25	83¼
	10.7	18.7	4.0	18		130	37	82¼
	10.2	16.0	4.2	21		70	52	81¾
		15.0	3.0	17		15		
			Death in coma.					

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CHART IV. CASE No. 4.

β-oxybutyric acid excreted.	Nitrogen.	Ammonia. Total.	Ammonia. % of nitrogen.	Urine, total sugar.	$NaHCO_3$.	Weight of Patient	Remarks.
gm.	gm.	gm.		gm.	gm.	lb	
0				520	10–20		
++				76	10–20	92	
0				312	10–20	100	
				170	10–20		
+-				165	10–20	108	
0				144	10–20		
0				357	10–20	105	
	18.5	2.4	14	276±			Coma began during last six hours.
56	23.8	3.7	11	167	113		Coma relieved 2 hours after onset.
96	18.7	3.7	20	233	140		Coma relieved.
70	2.1	5.3	25	61	92		Coma returns.
		0.8		10	6		Coma deepens; death.

CHART V. CASE No. 74.

Diacetic acid.	Nitrogen. grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Carbohydrate, balance.	Weight of patient, pounds.
0				30			92
+				0			
+++				21			
+++				69			
++							
+++				107			
++++	12.2	3.2	22	77	8		
++++		3.5		65	8		106
++++		5.8		103	8		104
		4.0		98	12	—32	

Death in coma, Dec. 16, 1907.

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Date.	Vol.	Diacetic acid.
	ccm.	
Dec. 10, 1902	1,360	0
Feb. 25, 1903	1,250	+(?)
Sept. 13, 1903		+
May 23, 1904	1,750	
June 9, 1905	2,000	++
Aug. 10, 1906	2,000	+++
Dec. 7, 1906	2,000+	+
June 25, 1907	3,500	+

Diabetes first

Date.	Vol. ccm.	All
1905.		
Nov. 15,	3,840	Sligh
Dec. 6,	2,520	,,
1906.		
Feb. 7,		
Oct. 6,	2,070	,,
,, 10,	3,180	,,
,, 12,	2,640	
Nov. 30,	.....	,,

Date.	Vol. ccm.	Diacetic acid.
1903.		
June 12,	2,100	0
1904.		
Jan. 27,	2,200	
Dec. 19,	1,690	0
1905.		
June 11,	1,120	+

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CHART IX. CASE No. 42.

Diabetes first observed in 1884.

Nitrogen.	Ammonia. Total.	Ammonia. Per cent of Nitrogen.	Urine, total sugar.	$NaHCO_3$.	Weight of patient.	
gm.	gm.		gm.	gm.	lb.	
			38		159	
			.0	4	159	
			0.2%	5	157	
			0			
			50	4	156	
			39			48 hyaline and 16 fine granular casts found in two cover glasses of centrifugalised sediment.
20.9	1.8	7	80		147	Partial hemiplegia (Nov. 27).
			112	April, 1907	153	
	Death in Coma, July, 1907.					

CHART X. CASE No. 101.

served in 1903. Best weight, 175 lb. Summer, 1905, 140 lb.

in.	Diacetic Acid.	Nitrogen, grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Weight of patient, pounds.	
race	++				154	12	132	
„	++				25		145	
						8	152	
„	+++				64		143	Few casts.
„	+++	19	3.5	15	80			
	+	14	2.7	16	73	12		
„	++					12		

Death in coma, February, 1907.

CHART XI. CASE No. 108.

Nitrogen, grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	Weight of patient, pounds.	
15.5			151		
			143		
21.2			46	146	
9.7			13	145	
9.9			50	146	
					April 18, 1906, 38 hyaline and 3 fine granular casts.
10.1	2.4	20	52		
9.6	2.8	24	70		June 21. weight. 138.

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April 18, 1906, 38 lysine
June 21, web int. 138

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Date.	Vol. ccm.
1906.	
Oct 9,	1,750
„ 15,	1,440
„ 16,	2,235
„ 18,	1,830+
„ 19,	2,190+
1907.	
Jan. 23,	
April 21,	

Bes

Date.	Vol. ccm.
1906.	
Aug. 18,	2,130
Sept. 26,	2,880
Oct. 12,	2,220
Nov. 6,	2,280
Dec. 4,	2,310
„ 18,	1,930
„ 22,	1,620
„ 26,	2,220
„ 31,	2,410
1907.	
May 15,	2,760
„ 16,	2,420
„ 17,	3,000
„ 18,	2,740
„ 19,	3,040
„ 22,	2,380
„ 23,	2,640

Date.	Vol. ccm.
1906.	
Sept. 26	

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CHART XII. CASE NO. 138.

Best weight, 145 lb.

Diacetic acid.	Nitrogen, grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Weight of patient, pounds.
+++	18.5	1.0	5	22	4	
++	15.1	1.7	9	29	4	
+++	21.7	1.5	5	39	4	
++	15	0.8	5	48	4	
+++	16.3	3.4	17	43	4	124
++++			20			
++		3.2		77	12	

Death in coma, July 12, 1907.

CHART XIII. CASE NO. 145.

Weight, 178 lb. Summer, 1906, 138 lb., then rose to 152 lb.

Diacetic acid.	Nitrogen, grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar, grams.	$NaHCO_3$, grams.	Weight of patient, pounds.
0	21.1			77		
0	21		8	104		
0	14		6	64		
0	15		5	77		
+	15		10	108		
	12.4			100	6	Dec. 15, 150
++	10.3	1.4	11	82	6	Dec. 23, 148
+++	13.2	1.6	10	79	6	147
++++	12.7	1.8	12	97	6	
+++		4.0		99	12	
+++		3.6		70	12	
+++		4.1		104	12	145
++++		3.6		101	12	
+++		3.4		102	12	
+++	10	1.7	14	55	12	
++	14.9	2.4	13	79	12	147

Death in coma, Sept. 2, 1907.

CHART XIV. CASE NO. 137.

Best weight, 157 lb. Weight, Sept. 25, 1906, 121 lb.

Diacetic acid.	Nitrogen, grams.	Ammonia. Total, grams.	Ammonia. Per cent of nitrogen.	Urine, total sugar.	$NaHCO_3$, grams.	Weight of patient, pounds.
+++				6%		Oct. 19, 121
++	15.2	4.7	26	grams 230	12	
+++	17.7	5.8	27	124	12	122

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we first saw them until death. No notable loss of weight was experienced by any patient. The cases illustrate the seriousness of a moderate acidosis in old people in comparison to the severity of such a condition in young individuals.

CONCLUSIONS.

1. Quantities of ammonia reaching 5 gm. in twenty-four hours indicate an extremely severe form of diabetes, which usually proves fatal within a year.

2. Patients under forty years of age tolerate an acidosis estimated in terms of 4 to 5 gm. ammonia far better than those above fifty years tolerate an acidosis of 2.5 to 4 gm. ammonia. An acidosis in an individual above fifty years of age is of very serious prognostic import.

3. A knowledge of the ammonia excretion usually helps in the treatment of a case of diabetes, and generally, but not always, gives warning of impending danger.

4. The value of a knowledge of the ammonia excretion in the prognosis of a diabetic patient is enhanced by a knowledge of the quantity of albumin and carbohydrate in the diet.

5. A lowering of the carbohydrate intake in a severe case of diabetes from a total of 80 gm. to 55 gm. in twenty-four hours produces little effect upon the acidosis.

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TABLE I.

		Grams, weight of fresh feces.	Grams, weight of dried residue.	Nitrogen, per cent.	Nitrogen, grams in feces.	Fat, per cent.	Fat, grams in feces.	Carbohydrates, per cent.
Case I. — One daily excretion on each of four days of experiment.	Feces of third day,	70.2	19.4	5.29	1.025	21.2	4.1	6.81
	Feces of fourth day,	89.4	21.1	5.01	1.05	23.2	4.9	7.05
Case II. — Excretion of first and second day. None on third and fourth days, excretion on fifth and sixth days. Diet continued six days.	Feces of fifth day,	226	57	5.4	3.07	24.1	13.6	
	Feces of sixth day,	54	12.1	5.04	0.60	23.2	2.8	

TABLE II.

	Weight of feces, average per day.	Weight of dried residue per day.	Nitrogen, per cent of dried residue.	Nitrogen, grams per day.	Fat, per cent of dried residue.
Case of jaundice: Examination of mixed three-day excretion.	315 gr.	59 gr.	4.14 Normal average, 5	2.49 Normal, 1 gr.	52 Normal, 20–35
Case of pancreatic disease? Examination of single daily specimen.	297 gr.	58 gr.	6.81		48

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this test diet is slightly less in young children than in individuals of greater age.

The findings of our experiment as regards the study of proteid utilization would, therefore, indicate that the capacity of function of normal individuals for the utilization of food proteid, under the conditions of diet in the experiment, is fairly uniform. From this fact it would appear that by the use of the method of investigation used in the experiment it should be possible to determine with considerable accuracy the existence or non-existence of any disturbance of the function of the absorption of proteid in any case under observation.

Examples of the possibilities of determination of the existence of a disturbance in the function of the utilization of proteid food by the method of study may be seen in the following records of two cases, in which the proteid finding was abnormal.

CASE I. Cancer of pancreas.

Microscopic examination: Great increase in quantity of muscle fiber over normal.

Total nitrogen, 7.81%.

CASE II. Enteritis with diarrhea: Microscopic examination showed quantity of muscle fiber normal, evidencing normal function of digestion of this proteid.

Total nitrogen, 8.05%.

According to our explanations in Table III, the increase of proteid in this case may be due to either an increase of food proteid or an increase

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of body proteid (diarrhea being present). No absolute deduction as to the function of proteid utilization can be made.

The finding of total fat contents of the feces which serve as the index of the utilization of fat in our experiment were as follows:

Average finding of 17 examinations upon 11 individuals,	28.5%
Minimum finding of 17 examinations upon 11 individuals,	19.2%
Maximum finding of 17 examinations upon 11 individuals,	39.5%
Extreme variation of all cases,	20.3%
" " in a single individual (two examinations),	9.3%

If we contrast the findings in the three cases of young children with those of the older children and adults, we find that the average is much the same. That is, it appears that the utilization of fat under this test diet is equally good in children and adults.

The findings of our experiment as regards the study of fat absorption would therefore indicate that the capacity of function of normal individuals for the utilization of food fat under the conditions of diet used in this experiment shows a considerable variation. And this extreme variation is not a matter of one exceptional case — one extremely low finding and one extremely high finding. The maximum figure is approached in several cases and the minimum in several cases.

Since this is the fact it would appear that absolute determinations of the existence of disturbance of fat absorption could be made by

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this method of comparison of the findings of the case under experiment with the normal findings only in cases where the normal excretion was large, so that a moderate deficiency in the absorption would increase the quantity of feces fat over the maximum normal limits, or in cases with a great deficiency of fat absorption. The variations in the quantity of fat in the normal are so extensive that it would appear perfectly possible for any normal individual whose capacity for utilization of fat was above the average to have a considerable deficiency of absorption of food fat, without increasing the quantity of feces fat above the normal limits. We can say in regard to any individual with symptoms of disturbance of intestinal function or of nutrition, whose feces show as the result of examination a fat content which is above the average normal; though still within the normal limits, that his feces findings suggest that a disturbance of the function of fat utilization may be a cause of his symptoms. But we can absolutely diagnose the existence of such a disturbance of fat function only in cases where the fat excretion transcends such maximum findings as are common in normal individuals.

This variation in fat content of the feces in the normal individuals on any definite diet is a well recognized fact. Thus v. Noorden found in the same individual upon the same diet a daily variation of from 0.5 to 4.5 gm.[9] It is clear that

[9] v. Noorden: Lehrbuch der Pathologie des Stoffwechsels, Berlin, 1893, sup. 7, S. 33.

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such a variation would show equally in results obtained by actual calculation of the average daily excretion in grams per day as by those of this per cent method of calculation.

The findings in regard to the proportion of neutral fat in the total fat content of our feces, which serve as the index of the digestion of fat in our experiment, indicate that the proportion of this substance to the total fat excretion is fairly constant in normal individuals. In no case was the proportion above one third of the total fat. The findings in this regard would indicate that the capacity for the digestion of fat in normal individuals under the diet given was fairly uniform. The method of examination should, therefore, enable us to determine the existence of any considerable disturbance in this function.

The records of carbohydrate excretion, which serve as the index of carbohydrate utilization in our experiment, were as follows:

Average finding of 7 individuals,	8.01%
Minimum „ „ 7 „	6.39%
Maximum „ „ 7 „	11.2%
Extreme variation in all cases,	4.81%

The variation found in these normal findings for carbohydrates is, if we take the minimum and maximum records, very considerable in proportion to the quantity of carbohydrates present. A further study of the records, however, reveals the fact that a discrepancy from the common finding exists only in the cases of the two young children examined, the findings of the older

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children and adults showing a fairly uniform character. The findings in the two children are both much higher than in the other cases, but are very similar to each other. The suggestion of this showing of our experiment is that the utilization of carbohydrates upon this diet is less good in younger children than in older persons. In using this method of examination for the study of function in the general run of clinical cases, therefore, we must use two separate sets of normal records for comparison, — one for young children and one for adults. If this course is followed, it would appear from the results of our experiment that the method provides fairly accurate means of determining the existence of any considerable disturbance of the function of utilization of carbohydrates, since the records obtained in normal individuals of the same general class as to age are fairly uniform. The number of observations made in regard to this point is, of course, too small to justify a decided statement to this effect. But as far as these records go this is the evidence: the extreme variation of the 5 cases of older children and adults being only 0.71%, the minimum finding 6.39%, and the maximum 7.1%, the average 6.78%, while the two cases of young children show records of 11% and 11.2%, respectively.

The finding in regard to starch remains as revealed by the microscopic examination of the feces, which serves as the index of starch digestion in our experiment, showed marked uni-

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other authors. For convenience we have classified them according to the week of the disease in which the culture was taken:

Week of disease.	Number of cases.	Culture: negative.	positive.
1	5	0	5
2	19	8	11
3	2	0	2
4	0	0	0
5	1	1	0
?	1	0	1
relapse,	2	0	2
Total,	30	9	21

In three instances in which we examined the blood in a relapse typhoid bacilli were found. It would thus appear probable that blood cultures would be a useful point in the differential diagnosis between relapses and complications.

Positive blood cultures are somewhat more frequently obtained in the severe than in the mild cases of typhoid fever. Kayser (*loc. cit.*) gives the following data:

Nature of typhoid cases.	Total cases.	Positive cultures obtained.
Very severe,	27	21 or 78%
Severe,	21	16 or 76%
Medium,	41	25 or 61%
Mild,	36	15 or 42%

The difficulty of classifying cases of typhoid fever in terms of severity is obvious. We have attempted to do it more from the general impression the individual made upon us than from any one arbitrary criterion. It would not be justifiable to draw far-reaching conclusions from such a small number of cases as we present in the following table:

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Nature of Typhoid cases.	Total cases examined.	Positive cultures obtained.
Severe,	9	8 or 88%
Medium,	15	12 or 80%
Mild,	6	1 or 16%

We repeatedly attempted to prove that mild cases of fever entering the wards were of typhoidal origin, but almost invariably failed to do so. In only one such case, in fact, were we successful. There is no doubt but that better results would have been obtained if the mild cases had been examined earlier. The severe cases were examined on an average by the eleventh day, the cases of medium severity on the twelfth day, but the mild ones, on an average, not until the sixteenth day.

It is certainly only fair to state that as time went on our experience improved, and it is quite possible that an occasional positive case may have been overlooked in the first part of our work. Improvement in technic, of course, was bound to occur. The time saved in investigating a single case was easily reduced two thirds, so that we feel the blood culture method of diagnosticating typhoid fever can be introduced as a routine measure.

The organisms from nineteen of the twenty-one positive cases gave all the typical reactions for typhoid bacilli. The organism isolated from one of the patients, who clinically did not differ in type from the others, produced gas in dextrose agar, to a slight extent in plain agar and had a more diffuse growth on plain agar than was the case with the other organisms, but the initial acid-

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ity in litmus milk persisted. This organism was uncommonly motile, shorter and of smaller diameter than the typical typhoid bacilli. It resisted clumping with the sera of many other typhoid patients except in a dilution of one to ten, and was not agglutinated even by the patient's own serum until thirty-three days from the onset of the disease, and only then in a similar dilution. This patient's serum also failed to clump the laboratory stock cultures of typhoid bacilli except in a dilution of one to ten. It also completely failed to clump the laboratory stock cultures of alpha- or beta-paratyphoid bacilli except in the same dilution. v. Hösslin[6] has recently reported cases of this character. This case illustrates the advantage which the cultural method of diagnosis has over the agglutinative reaction.

The organisms of another case gave all the positive reactions for typhoid bacilli except that after the initial acidity was produced the latter changed back to a deeper blue than before. The changes in the acidity of the milk produced by this case (Gay) as well as by the previous case (Roan) are merely qualitative reactions and do not determine the classification of the organism.

The following tables show the variations of these two organisms in acidity and gas formation with the different sugar media in comparison with typhoid and alpha- and beta-paratyphoid bacilli. Plain bouillon was used from which the sugar was removed by the colon bacillus. To portions of this were added one per cent of lactose,

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saccharose, mannite, dextrin, maltose, galactose and dextrose. The fermentation tubes used were those devised by Theobald Smith to whom we are indebted for many suggestions.

TABLE OF ACIDITY AFTER INCUBATION FOR FORTY-EIGHT HOURS.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-para-typhoid.	Beta-para-typhoid.
			No. of ccm. of $\frac{N}{100}$ NaOH used.			
Plain,	0.6	0.8	0.8	0.8	0.7	0.4
Lactose,	0.7	0.9	0.7	0.9	1.0	0.8
Saccharose,	0.8	0.7	1.0?	0.6	0.7	0.6
Mannite,	0.5	3.4	3.4	3.6	3.5	4.1
Dextrin,	0.6	0.8	1.3	1.2	1.3	1.0
Maltose,	0.6	3.3	3.3	2.8	3.0	3.6
Galactose,	0.7	3.4	3.6	2.6	3.1	3.8
Dextrose,	0.6	3.6	3.6	3.9	3.8	4.5

TABLE SHOWING GAS FORMATION AFTER FORTY-EIGHT HOURS' INCUBATION.

Bouillon.	Control.	Typhoid.	Gay.	Roan.	Alpha-para-typhoid.	Beta-para-typhoid.
Plain,	0	0	0	0	0	0
Lactose,	0	0	0	0	0	0
Saccharose,	0	0	0	0	0	0
Mannite,	0	0	0	+	+	+
Dextrin,	0	0	0	0	0	0
Maltose,	0	0	0	+	+	+
Galactose,	0	0	0	+	+	+
Dextrose,	0	0	0	+	+	+

From the quantitative results shown in the above tables, it is evident that Gay's organism agrees well with the typhoid organism, except that it produces a higher acidity in dextrin bouillon. In the table showing gas formation it corresponds throughout with the typhoid.

Likewise, it will be seen that the organism obtained from Roan agrees with the paratyphoids

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in acidity, especially alpha-paratyphoid, with which the greatest difference is but 0.5 ccm. in galactose bouillon. In gas formation this organism is identical with the paratyphoids.

Control tests were invariably made in the gas formation and acidity tests and were repeated until constant results were obtained.

HOSPITAL TREATMENT OF PATIENTS WITH TYPHOID FEVER.

Typhoid fever caused nearly six times as many deaths in Boston during 1907 as it did in Munich during 1906, yet the two cities have about the same population. Other cities in Germany and England also show much less typhoid fever than does our city. The record is still more unfavorable if we go farther back, because the year 1907 showed the smallest typhoid death-rate which Boston has so far attained.

The recent lowering of the typhoid death-rate has been brought about in this vicinity chiefly by hygienic measures of a general nature — such as closer inspection of water, milk and shellfish, both by the city and state authorities. Little has been done to prevent contact infection which Conradi and others have demonstrated to be the source of about one-fourth of all cases. It would therefore appear that the prevention of contact infection was the factor which demanded especial attention here at this time.

Two opportunities are open by which contact infection can be avoided: first, the early diagnosis

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of typhoid fever, and second, the detection of the bacillus carrier.

We have already alluded to Conradi's work which has shown that typhoid is especially contagious in the first week, and have demonstrated that by blood cultures an early diagnosis is possible. We are glad to again call attention to the fact that the Boston Board of Health is prepared to furnish blood culture outfits to those desiring them. Yet by this means only a portion of the contact infections can be avoided. The other source, the bacillus carriers, is entirely overlooked. With commendable energy, however, the State Board of Health has undertaken work along this line also and we undoubtedly shall hear much of it soon.

Fifty-five per cent of all diphtheria cases occurring in Boston during 1907 were treated in the South Department of the Boston City Hospital, and similarly fifty-four per cent of all fatal cases of typhoid fever which occurred in the city during the last five years were treated at one or the other of the three large hospitals. This is as it should be, because immediate contact infection is thereby reduced. That the practitioners in the city thoroughly approve of this course is shown by the large number of doubtful cases which they send to the Boston City Hospital, one third of the cases admitted with the diagnosis of typhoid fever in the course of seven months last year proving not to have the disease.

It is probable that the per cent of cases of ty-

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phoid fever which will be treated in the large public hospitals will increase, and for several reasons. Typhoid fever is a very expensive disease in private life. The duration of the illness, the necessity for at least one and usually two nurses, the two daily visits of the physician, or even the need of a doctor in constant attendance, and the frequent calls for specialists of one description or another contribute to this end. The cost is not lowered by sending typhoid patients to a private hospital. These hospitals consider such patients so undesirable that they demand rigid isolation with absolutely no contact between them and the nurses of other patients. Indeed, several of the private hospitals absolutely refuse to admit typhoid patients at all, because the surgeons, who chiefly patronize such institutions, will not tolerate the chance of infection of their own surgical cases with typhoid fever. Only wealthy patients can enjoy the privilege of being treated for typhoid fever in a modern manner in their own homes.

The large institutions on the other hand are well adapted to the care of typhoid fever. They contain many wards, and it is a simple matter to so group the typhoid patients that infection of other patients and attendants can be reduced to a minimum. The isolation of typhoid fever patients in hospitals was provided for in Germany in 1905.[7]

Nurses should be protected during the care of typhoid fever patients in hospitals. In a former paper[8] we showed that nurses working in six hospitals in Massachusetts were eight times as liable

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to contract typhoid fever as the ordinary citizen, and that hospital ward tenders under the same circumstances were thirteen times as apt to acquire the disease.

This last year (1907) forty-seven nurses in the State of Massachusetts have been thus attacked, while the total number of reported cases of typhoid fever in the state was two thousand three hundred and eighty-nine. Another year might not show that for every group of fifty typhoid patients a nurse developed the disease, but we think this not at all unlikely. Only ten of these nurses apparently contracted typhoid fever in private nursing, but thirteen of the hospital nurses, it is only fair to say, were infected by an early unrecognized typhoid case in a nurses' dining-room. It does not seem justifiable to expose twenty-three female nurses, fifteen male nurses and thirteen physicians on one day in the same institution to the risk of contracting typhoid fever from twenty-eight typhoid patients when a hospital possesses many wards and rooms into which these patients could be gathered and cared for by a third of the above number of attendants.

Isolation in separate wards is not by any means the whole story. Early diagnoses to determine when to isolate are essential. Fortunately, by the use of blood cultures, the early diagnoses are the ones most easily made. The possibility of making an early diagnosis probably decreases about five per cent a day after the first few days until well along in the second week when the Widal test be-

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comes rapidly more and more positive. On comparing the dates upon which we made blood cultures with the dates of admission of these same patients to the hospital, we find that we lost on an average two days of time. This shows the need of such work being performed by those living in the hospital rather than by voluntary workers from outside. An early diagnosis demands much time, and allowance must be made for this in the organization of a medical clinic.

If it is really intended to stamp out typhoid from the community, patients should not be discharged from the hospital without a knowledge on the part of the health authorities as to whether they are typhoid carriers. The time at which the typhoid bacilli disappear from the stools and urine is a variable factor, and as far as the stools are concerned an uncontrollable one. It is perfectly feasible, however, to determine whether patients are free from bacilli. German regulations require isolation, when bacilli persist in the stools, until ten weeks after the beginning of the disease; after this period special rules are provided for those who may still be bacillus carriers. As yet no such regulation exists in Boston or Massachusetts, but a knowledge of the presence or absence of typhoid bacilli in the stools would exert much influence upon the date recommended for the discharge of a patient. Such work would demand much time, but it would represent a high standard of preventive medicine.

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CONCLUSIONS.

1. Our data agree with those of investigators having much larger series of cases, namely, that typhoid fever generally can be diagnosticated in the first week by use of blood cultures, but that this method yields positive results in only about sixty per cent of the cases in the second week.

2. The typhoid bacilli are most easily obtained by blood cultures from the severest cases.

3. The typhoid bacilli were found in the relapse of typhoid fever in three individuals.

4. Typhoid fever is becoming more and more a disease to be treated in the larger public hospitals.

5. Isolation of typhoid fever patients in hospitals for the sake of other patients and particularly for the nursing staff is demanded.

6. Early diagnoses on entrance to the hospital and the detection of bacillus carriers before discharge are requisites in the present campaign against typhoid fever.

We wish to express our appreciation of the courtesy extended to us in our work by Dr. George B. Shattuck, Dr. John L. Ames and Dr. John Bartol who placed all their typhoid patients at our disposal, and to Dr. Francis H. Williams and Dr. Horace D. Arnold from whom we obtained special cases. The work would have been impossible without the co-operation of Drs. Rhea, Mabee and Bosworth of the Pathological Laboratory to whom we feel much indebted as well as to Dr. Adler for helpful suggestions.

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THE USE OF TUBERCULIN IN THE TREATMENT OF LOCALIZED TUBERCULOSIS EXCLUDING PULMONARY TUBERCULOSIS.*

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THE treatment of tuberculosis with the various products of the tubercle bacillus is nearly as old as the discovery of the specific cause of tuberculosis. A considerable mass of evidence has been collected concerning the therapeutic use of tuberculin in various ways. More recently, Trudeau and his associates at Saranac Lake have argued that the end to be attained was immunity against the tubercle bacillus. Some facts of animal experimentation also seem to favor this view. Those observers have reported a considerable series of cases of pulmonary tuberculosis showing the value of increasing doses of tuberculin. Sir A. E. Wright, of England, has utilized the theory of phagocytosis. He believes that in cases favorable for treatment, which are essentially localized tuberculosis, there is a deficient amount of opsonins, those substances in the blood which prepare the bacteria for ingestion by the leucocytes. According to his theory tuberculin acts

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by increasing the amount of opsonins, and the treatment should be controlled by the determination of the opsonic index.

It is not the purpose of this paper to discuss the theories of the action of tuberculin but to give the results obtained in a series of cases of localized tuberculosis. There were 25 cases, divided as follows: 9 cases of tuberculous adenitis, 4 cases of lupus vulgaris, 4 cases of tuberculosis of the genito-urinary tract, 3 cases of tuberculosis of the wrist, and 1 case each of tuberculosis of the knee, tuberculosis of the spine and pelvis, tuberculous sinus, tuberculous fistula in ano, and erythema induratum. As far as known no cases of pulmonary tuberculosis are included. In the early cases the opsonic index was determined as a routine, as a rule, twice a week. Of the cases included in this list, the opsonic indices were followed in 9 for varying lengths of time during the treatment. Seven were followed for over four months. Four cases (I, II, XI and XIII) showed an opsonic index of 1 or above, at two or more observations at the beginning of treatment. According to the rules laid down by Wright they were not satisfactory cases for treatment. However, they were not doing well at the time. Nevertheless, under treatment by tuberculin, 3 of the 4 showed a most satisfactory result. In 5 cases (X, XIV, XVIII, XIX and XXIII) the initial observations were distinctly below normal. All these 5 are classed as distinctly benefited. In none of the 9 cases was a marked tendency for the opsonic indices to follow any

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particular curves noticed. As a rule, it should be said, however, that if a case was doing badly the index was often low, but not invariably so. The clinical manifestations were markedly more accurate. At first, attempt was made to reinoculate at the time advised by Wright, that is when the opsonic curve was descending to normal. This was soon found to be impracticable, and for the last several months no opsonic indices have been determined in any of the cases under treatment. Cases which have been put under treatment since that time have apparently done as well as the others. The old cases have apparently done as well without the opsonic index as with it.

Dr. Roger Kinnicutt and the writer made some comparative opsonic index determinations, using different preparations of bacteria, white corpuscles and sera. In all the cases of which I have record, 10 in number, the greatest difference was in hundredths, using 1 as the standard. There were observations on a number of cases which were not treated. In all cases, at least four indices were determined over a period of two weeks. Twenty-three cases, obviously tuberculous, presented a fluctuating index beyond 0.8 and 1.2. Four cases, with the clinical diagnosis of probably a non-tuberculous disease, presented similar fluctuations. One of these is Case XXIII, in whom, it seems to me, we have a therapeutic diagnosis. Another was a case of a knee which was treated by request with vaccines of the gonococcus without change. A guinea pig inoculated with tissue

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from that knee showed tuberculosis. Another, clinically, was a case of Hodgkin's disease, in whose sputum typical tubercle bacilli were subsequently found. The fourth was a patient with a mediastinal tumor who gave a positive tuberculin reaction. There were 5 cases of obvious tuberculosis, whose opsonic indices did not vary from normal limits. There were 3 cases in whom the clinical diagnosis of probable tuberculosis was made, whose opsonic indices did not vary from normal limits and who gave no tuberculin reaction. Five milligrams of old tuberculin were finally given in each case.

There were 3 cases of especial interest. The serum of an interne at the Massachusetts General Hospital was used on two occasions as control. Compared with my own serum his opsonic index was 0.6 and 0.65. The discrepancy was attributed to an error in technic. Two months later he had pulmonary hemorrhages. One case was seen in May, 1907, with a diagnosis of the tuberculous glands of the neck. Four different observations showed her opsonic index to range between 1.1 and 1.3. She was kept under observation but not inoculated, since at that time it was considered that she was manufacturing enough opsonins and ought to get well spontaneously. Her general condition improved. The glands of her neck became much smaller. She then passed from observation until February, 1908. At this time she presented enlarged glands in the left axilla, which were apparently

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about to break down. She has been started on tuberculin but has been under observation only two weeks. The third case was a case of acute tuberculous pleurisy. Clinically the case was steadily failing and a bad prognosis was given. The opsonic index was continually over 1.2. After a period of three weeks, improvement set in and the disease was apparently arrested. The conclusions from the work on the opsonic index in connection with tuberculous disease are that the opsonic index has no value as a therapeutic indicator; that it may be of some value in diagnosis and prognosis, but it is certainly not reliable. Two observers will get approximately the same results.

In the cases about to be reported, no case has been under treatment less than four weeks. No case was taken unless it was doing poorly from the clinical point of view. In every case due attention was paid to the necessary doctrines of fresh air, food and general hygiene. Most of the cases, however, have continued their same mode of life without essential change. The diagnosis has been, of course, unfortunately clinical in nearly every case. Nevertheless, there seems to be doubt of diagnosis in no case, In every case the diagnosis was confirmed by at least one other observer.

The preparation used was tuberculin, B.E. The initial dose has varied from 1-10,000 to 1-1,000 of a milligram. The doses have been graded always to avoid any reaction, either con-

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stitutionally or in the local lesion. In only 2 cases has there been any increase of dosage over 1-1,000 mgm. The dosage has been increased only when the case seemed to be standing still. There are a few cases which have been under treatment for nearly a year which are still improving on a dosage of 1-1,000 mgm. and have shown no signs of immunity. As far as known there have been no rises in temperature. On several occasions there have been constitutional reactions of headache and malaise in the twelve hours following inoculations. Occasionally, fairly well-marked local reactions at the site of the tuberculous lesion were seen. The most marked example was in Case XIX. A dose of 1-4,000 mgm. caused, first, a marked increase in a local lesion, and then breaking down and discharge, all within two days. Any such reactions were regarded as indications to decrease the dose. The inoculations have been given subcutaneously, chiefly in the back and abdomen. There have been no untoward effects at the site of inoculation beyond a trifling discomfort in some apparently susceptible cases. As a routine, cases have been inoculated once a week until the disease was apparently arrested. There was observed in no case any objection on the part of patients to the inoculation.

There were nine cases of tuberculous glands:

Case I. M., a young woman of twenty-three, gives a history of glands in the left axilla which were lanced

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sional single nodule appears. The color is a dark red. The scarring is very smooth and soft. Curiously, on the right side of the face, which was least involved, the result has not been so good, but the very marked improvement of the appearance of the face leaves no doubt of the great benefit derived from the tuberculin treatment. Whether this obstinate case will be ultimately cured is still an open question.

Case XI. E., a young woman of thirty, has had an extensive lupus of the nose and adjacent part of face and mucous membranes of the nose and mouth for eleven years. Under the most efficient treatment available the disease had steadily progressed. She was first seen in May, 1907. She was given 1-2,000 mgm. tuberculin, and was inoculated at weekly intervals for eight weeks with marked improvement. She was better than she had been at any time for ten years. Inasmuch as she lived so far from Boston she was given some tuberculin with instructions for inoculations by the local doctor. Improvement continued for a month. After that time the inoculations were given very irregularly, often two weeks going by without an inoculation. With the irregularity of the inoculations, improvement ceased, and after two months, treatment was abandoned. This case was not benefited, but the improvement with regular inoculations and the cessation of that improvement when the inoculations became irregular, seem to suggest a possible reason for the failure.

Case XII. H. L., a boy nine years old, had lupus of the wrist in 1901 and which began on the neck in 1902. Since 1904 he has been under treatment for Pott's disease. He was first seen April 23, 1907. At that time he had a lew lupus nodules in an extensive white scar of neck and chin. Over an area, 6 x 3 in., on the right wrist was a crusted lupus lesion. He was

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inoculated at weekly intervals from April 24 to Aug. 17. The dose was increased from 1-2,000 mgm. to 1-1,000 mgm. On Aug. 17 he showed no lupus nodules and presented a smooth, white scar both on wrist and chin. He was given 1-1,000 mgm. at about two weeks' intervals from Aug. 17 to Oct. 25. At that time there was no recurrence. He disappeared from observation until Dec. 7. At that time a few new lupus nodules were starting on his wrist. He was re-inoculated, but has reported only at very irregular intervals since. At the present time he has numerous, new crusting lupus lesions in the scars of his neck and wrist. The boy lives among the most unfavorable environments. This case is one presenting a recurrence which it seems possible might have been averted had the boy reported regularly for inoculation. It certainly shows importance of close observation of cases and the necessity in some cases of continuing the inoculations after the disease is apparently arrested to avert recurrence.

Case XIII. C. B., a boy eleven years old, has had an increasing patch of lupus vulgaris on his left cheek for seven years. This patch had slowly spread, despite the usual efficient treatment. He was first seen on April 23, 1907, when he presented a circular patch on his cheek about four inches in diameter. There were numerous red, active, new lesions. He was inoculated weekly from April 23 to July 28. The dosage was increased from 1-3,000 to 1-1,500 mgm. On July 28 the patch presented for the most part a smooth scar with only a small rim of ulcerated tissue on one half the circle. The physician in charge of the skin department stated that he was better than at any time during the four years he has been under observation. It was thought advisable to remove the small remaining rim of diseased tissue with curette and cautery. The boy

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then reported not oftener than once in six weeks. He was seen on Feb. 8, 1908, when his lesion was entirely healed. Inoculations every two weeks had been urged upon the boy but he had not reported for them. Tuberculin seems to have had some part in the arrest of this disease. This case is in notable contrast to the preceding case, as this boy went without inoculations without recurrence. It should be stated, however, that the boy has better home surroundings; his general condition is far better and he shows no other lesions of tuberculosis.

There were four cases of tuberculosis of the genito-urinary system:

Case XIV. G. P., a man of thirty-three, has had pain and frequency of micturition since October, 1906. Since March, 1907, his urine has been cloudy and at times has contained clots. No other symptoms. The man is athletic and has worked hard. Rectal examination is negative. Urine contained pus, blood and tubercle bacilli. A guinea pig inoculated with the urinary sediment showed tuberculosis. Inoculations were begun on Nov. 25, 1907. The dosage was slowly increased at weekly intervals from 1-10,000 mgm. to 1-1,000 mgm., which he is now receiving. There has been little change in the local condition. The frequency is about the same. Pus and tubercle bacilli remain in the urine. There has been considerable improvement in the general condition. For some time previous to the inoculations his weight has been steady at 155. Without any other change, he now weighs 160, his best weight. He says he feels better than for years. This case is classed as doubtfully benefited. This case is a patient of Dr. Wilder Tileston, to whom I am

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indebted for notes of the case and permission to include it in this series.

CASE XV. L., a young man twenty-one years of age, has noticed increasing frequency of micturition for the past year. When first seen on Oct. 31, 1907, he got up five times at night to urinate and urinated every one and a half hours during the day. There was considerable pain on micturition. His urine contained much pus. A guinea pig inoculated with the urinary sediment died of tuberculosis. On examination, his external genitals are normal. There is a nodule in the right lobe of the prostate. The right kidney is palpable and large, somewhat tender. On cystoscopic examination an injected bladder was found but no ulcers. He was not considered a case for surgical interference. Beginning with 1-4,000 mgm. the dosage has been increased on weekly inoculations to 1-1,000 mgm. At the present time he gets up either once or twice at night to urinate, and urinates during the day every two to three hours. There has been no pain on micturition after the first three weeks of treatment. There has been a gain of weight of about ten pounds. The man has kept at work. He says himself that he feels vastly better than at any time for two years. His comfort is apparently insured by stopping the frequency of micturition. His urine still contains the same amount of pus. This case seems benefited. The most conspicuous change has been the improvement in general condition.

CASE XVI. La., a young man of twenty, four years ago, had frequent and painful micturition with pus in the urine. For the last three years the pus has continued in the urine, but the frequency and pain have not been so marked. On cystoscopic examination the bladder seemed normal and pus was seen coming out

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of the left ureter. At that time, September, 1907, the testicles and prostate were normal. On Sept. 10, 1907, a tuberculous left kidney was removed. The wound healed slowly. Beginning Oct. 17 he received weekly inoculations of tuberculin, the dose being increased from 1-3,000 to 1-1,500 mgm. The wound rapidly healed, but perhaps a more important feature than the tuberculin was the removal of several silk sutures. However, there was a gain of ten pounds in weight. The man is now at his maximum weight and working every day. He has no urinary symptoms. There is still microscopic pus in the urine and a few tubercle bacilli. On Feb. 7, 1908, his left testicle, which became swollen immediately after the operation before the tuberculin was given, again became swollen. His dosage was immediately cut from 1-1,500 mgm. to 1-3,000 mgm. At the present time the testicle is rapidly growing smaller. It cannot be definitely stated that this case was benefited by tuberculin. It seems probable that the use of rather large doses (1-1,500 mgm.) stirred up the process in the testicle. There has been, however, a marked improvement in the general condition.

Case XVII. Ma., a man of thirty-three years old, gives a history for the past six years of backache, and frequent, painful micturition, and pus in the urine. In August, 1906, a perinephritic abscess was drained, which left a persistent sinus. Since that time his frequency and pain in micturition increased and he no longer had control of his urine. He lost weight and was unable to do steady work. Cystoscopic examination showed a small injected bladder without ulcers. Testicles and rectal examination were negative. Tuberculin reaction was positive. Nov. 22, 1907, his left kidney was removed. Pathologically, it showed typical

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appearance of tuberculosis. After the operation the frequency and lack of control of the urine persisted, and on Jan. 13, when first seen, he presented a large sluggish wound in his kidney region. Beginning with 1-4,000 mgm. he has received weekly inoculations up to 1-1,000 mgm. At the present time the wound has healed. He still has some lack of control of urine at night, but is able to hold his urine three or four hours in the daytime. There is no pain. The urine still contains pus and tubercle bacilli. The most marked change has been in the general appearance. In a little over six weeks he has gained fifteen pounds, and he is now doing a full day's work as painter. He states that after the inauguration of the inoculations of tuberculin he began to feel generally better and now is better than he has been for six years. While the local condition is apparently the same, there seems no doubt that the man's general physical condition has markedly improved.

There were three cases of tuberculosis of the wrist:

Case XVIII. Ch., a woman of forty-five, had had a painless swelling on the back of the right wrist for over a year. This swelling was removed at operation in March, 1907, and the mass proved to be tuberculous. She was first seen May 14, 1907. At that time she presented a clean scar with a considerable mass of indurated tissue about it. This mass had been increasing for the past three weeks with an increase of pain. She was given six inoculations of 1-1,000 mgm. at weekly intervals. At the end of that time there was no pain in the wrist, no induration, the motion was free. She was then discharged to go into the country. She was again seen in January, 1908, and had no symptoms or signs of recurrence. This case is re-

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garded as probably arrested, although there might be some room for doubt as to the nature of the induration and pain coming on several weeks after the operation.

Case XIX. G., a young girl of ten, gave a history of injury to the right wrist in December, 1906. This was soon followed by a painless swelling over the fourth and fifth metacarpal bones. She was treated by plaster fixation and Bier's hyperemia for two months without change. She was first seen April 8, 1907. At that time she presented a painless fluctuating mass the size of a golf ball on the back of her hand. On April 12 she was given 1-4,000 of tuberculin. The lesion promptly became larger, broke down within the next forty-eight hours. There were apparently well-marked constitutional symptoms also. The inoculations were kept up at ten-day intervals, the dosage being increased to 1-2,000 mgm. On June 21, the splint was omitted but the child did not keep the hand quiet. The induration of the back of the hand persisted. The splint was re-applied July 26. From that time on improvement was rapid. The splint was again omitted on Sept. 20. At that time there was present only a smooth scar on the back of the hand and considerable diffuse induration. She was then given inoculations at two weeks' intervals until Nov. 22, 1907. At that time very little difference between the two hands was noticeable. There was no deficiency in motion. Unfortunately, none of several x-ray plates were satisfactory. There were no inoculations after Nov. 22. The child was again seen two months later and the condition remained the same. This case is regarded as arrested.

Case XX. M. M., a woman forty years old, who had pain and swelling in both wrists in January, 1906. Operation in September, 1906, when considerable

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tuberculous material was excised from the anterior surface of both wrists. Tuberculin test was positive. She went into the country for six months. Considerable swelling still remained in both wrists but no pain. She started in work but the pain and swelling in the wrists increased. She was first seen Dec. 5, 1907. At that time she presented two clean scars in both wrists. In the left wrist there was a little swelling but no pain. There was fair motion of the left hand. The right wrist was markedly swollen. There was considerable pain, increased on motion and some swelling of the thenar eminence. There was marked limitation in motion of all the fingers. She has been inoculated at weekly intervals, the dosage being increased from 1-4,000 mgm. to 1-1,000 mgm. at the present time. There is now no swelling of the left wrist. The motion and strength of the left hand are apparently normal. The right wrist is still considerably swollen, although less so than at the inauguration of treatment. There is much less pain in the right wrist than at the beginning of treatment. There is marked improvement of the general condition, despite the fact that she does hard work in domestic service. This case is classed as doubtfully benefited.

There was one case of fistula in ano:

Case XXI. Bu., a man of fifty, has had a fistula on either side of the anus for four years. Has had several abscesses and several operations, including radical ones, for the cure of fistula, but the fistulæ have never been healed. He was first seen Oct. 20, 1907, when he presented large wounds on either side of the anus. Beginning with 1-2,000 mgm. of tuberculin he has had weekly inoculations and now is getting 1-1,000 mgm. The fistula has closed on one side and is appar-

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ently healing in well on the other. There have been no untoward symptoms since the beginning of the treatment. Again in this case there has been marked improvement of the general condition.

There was one case of persistent sinus after operation for tuberculous peritonitis:

Case XXII. B. G., a young woman of nineteen years, had an operation for tuberculous peritonitis six months ago, which left a persistent sinus. Beginning Feb. 6, 1908, she received tuberculin weekly beginning with 1-10,000 mgm. and increasing 1-10,000 every week. The environment of this case was changed for the better. Her general condition has been much improved. There has been marked gain in weight and strength. The discharge from the sinus is now spasmodic and averages much less. This case has been doubtfully benefited by the tuberculin.

There was one case of erythema induratum:

Case XXIII. O'D., a young woman of twenty-five years of age, has had psoriasis for years. When a child she had some "scrofulous glands" of which she now has only the clean scars on both sides of her neck. For a number of years on both legs she has had varying sized lesions of erythema induratum which have ulcerated and formed scars. In that time her legs have never been free from ulcers. In the winter time the lesions are more numerous. She has had various treatments, including active specific treatment. There was some doubt concerning the diagnosis of this case, and Dr. Roger Kinnicutt observed her opsonic index for the tubercle bacillus from April 3 to Aug. 10. I am indebted to him for his notes and his permission to include the first part of this case. The first four

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determinations of the opsonic index showed an index well below normal. She was then given tuberculin, starting in with 1-2,000 mgm. For several weeks there was no special change. Since that time the improvement has been steady. She now requires inoculation of 1-750 mgm. every seven days. On two occasions she has gone without inoculation for nine or ten days and very promptly on the eighth or ninth day new lesions have appeared. The last appearance of a new lesion was on Feb. 24, when she had been nine days without inoculation. Before that time she had been two months without any lesion, a thing which she does not remember to have happened since the onset of this disease. It is to be remembered also that she has more lesions in the winter time. This case is to be classed as distinctly benefited. It is of considerable interest, however, to note that the inoculations apparently have got to be kept up, although she has been under treatment for ten months, and at one time the disease seemed arrested. The psoriasis was unaffected.

There was one case of tuberculosis of the knee:

Case XXIV. J. B., a girl twenty-four years old, seven years ago had an excision of the right knee joint for tuberculosis. About Jan. 1, 1907, the left knee became swollen and somewhat painful on motion. There was no limitation in motion. She did not improve under best of general hygienic and local treatment. About Dec. 15, 1907, she had some pain localized to two red areas on the outside of the knee. On Jan. 9, 1908, she was given 1-10,000 mgm. She has had weekly inoculations to the present time, the dosage being increased 1-10,000 mgm. at each inoculation up to 1-1,000 mgm. On Jan. 25, she presented a sausage-shaped swelling along the outside of the knee joint,

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which distinctly fluctuated and which apparently was outside of the knee joint. The swelling was incised on Jan. 31, and pus evacuated. After the evacuation of the pus, the knee joint itself was very little swollen and not at all painful on motion. There has been some constant discharge from the incision but no swelling of the knee joint. Under precisely the same conditions as before tuberculin was given she has gained seven pounds in weight. Before that time her weight had been stationary for three months. It is problematical how much the tuberculin had to do with the change in the picture. It seems possible that the formation of this localized abscess was hastened by its use. The general condition and the local condition, which had been at a standstill for several months, are now certainly better. This case is classed as doubtfully benefited.

There was one case of tuberculous spinal and pelvic caries:

Case XXV. V., a woman twenty-nine years old, had, one and a half years ago, a left ilio-psoas abscess which was opened in March, 1907. She was in a plaster cast for some time. This ilio-psoas abscess has continued to drain. She presented a rigid back, but no knuckle. She came under observation Oct. 2, 1907, and was running a continuous temperature. She received 1-3,000 mgm. on Nov. 3, which was increased, by weekly inoculations to 1-1,000 mgm. on Nov. 24. The temperature came down. The discharge increased, but on Dec. 1, 1907, a fluctuating mass appeared over the crest of the right ilium, which increased in size with variations in temperature. The abscess was opened on Jan. 2, 1908. At that time apparently bare pelvic bone was felt. The temperature still showed

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wide excursions. On Jan. 16, 1908, she was again given tuberculin, this time with the initial dose of 1-10,000 mgm., which was increased at weekly inoculations 1-10,000 mgm. to 1-1,000 mgm. Since the second inauguration of tuberculin the temperature has drifted to normal and there has been some improvement in the general condition. The history of this case suggests the possibility that the tuberculin stirred up increased suppuration as evidenced by the formation of the second abscess. There seemed to be some slight improvement in the general condition. On the whole it cannot be said that this case received any benefit from the inoculations of tuberculin.

Of course, too short a time has elapsed to draw any permanent conclusions from the results as seen in this very small series of cases. Many of the cases are still under treatment. Experience also has shown the fallacy of definitely designating any case of tuberculosis as cured, no matter how long the interval of quiescence. The following conclusions, however, seem justified. Of 25 cases of tuberculosis localized elsewhere than in the lungs, treated with tuberculin, B. E., 6 cases were classed as arrested; 12 as distinctly benefited; 5 as doubtfully benefited; and 2 as uninfluenced by tuberculin. The most striking feature is that practically all of the cases showed a marked gain in a general condition, thus enabling them better to combat the local disease. The local condition was certainly markedly benefited in the cases of tuberculous glands and lupus. In the cases of genito-urinary

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at autopsy a careful search revealed no parasites these forms were probably vegetable cells.

March 25. There was dullness, especially marked, at the base of the right lung, with bronchial breathing and fine and medium sized moist râles. Fine and medium sized râles were scattered throughout the chest.

March 26. Examination of the blood showed: hemoglobin 35% to 40%. A differential count of 500 white cells showed:

Polymorphonuclear neutrophiles,	50.2%
Small lymphocytes,	4.0%
Medium sized lymphocytes,	.8%
Large lymphocytes,	.4%
Transitionals,	1.0%
Myelocyte (?),	.2%
Eosinophiles,	43.4%

In this count 9 normoblasts were seen (one with a divided nucleus). Besides these others were seen with two or three divisions to the nuclei, and one megaloblast. The red cells showed some variation in shape and size, an occasional macrocyte, frequent microcytes and some poikilocytosis. There was considerable achromia.

March 27. Considerable edema of lungs. Pulse gradually became weaker, and respiration more labored. The patient died at 11.15 A.M.

While he was in the hospital his temperature ranged somewhat irregularly between 100° and 102.6°, his pulse varied from 120 to 136, except on the day of admission, when it was 144, and his respirations were between 32 and 40, and on all but the first and last days were nearly uniformly 34.

The autopsy was performed March 27, 1907, four and a half hours after death.

Anatomical diagnosis: Hodgkin's disease; involve-

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ment of the cervical, axillary, inguinal, mediastinal, retroperitoneal glands, and glands of the lesser curvature of stomach, involvement of the liver, spleen and lungs. Persistent thymus gland.

A well developed and poorly nourished white boy. Length, 5 ft. 3½ in. Some suggillations of the posterior surface of the body. Pupils moderately dilated. Considerable edema of face, hands, feet and legs, and a little of the trunk.

The *thymus* gland was found persistent and enlarged. It was swollen and infiltrated.

The *pericardial* cavity contained four or five ounces of clear fluid.

The *heart* weighed 200 gm. and showed no valvular changes.

Glands of above-mentioned regions were enlarged, of firm consistency and discrete. Sections of three of these, as of other organs, were mounted in paraffin, and some stained by Unna's method with methylene blue and eosin, and some stained with Wright's modification of Leischman's stain. As a rule the eosinophiles stained better with the latter, but one or two specimens, stained by Unna's method, show them best; and the sections as a whole are better when stained in this way. Specimens fixed in celloidin and stained by hematoxylin and eosin failed to show any eosinophiles for some reason, so these specimens were all passed back through alcohol and remounted in paraffin.

Sections of a bronchial lymph gland from the neighborhood of the right bronchus show a marked hyperplasia of new formed tissue. As a whole, the glandular structure is lost. While certain areas show a predominance of lymphoid cells, yet the follicular character is gone, and there is a well defined hyperplasia through-

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out. The capsule is thickened, but there are no fibrous septa.

Microscopically, the gland consists of a minimum of reticulum in which are spindle and oval or epithelioid cells of various sizes, some plasma cells and giant cells containing two or three to six or eight nuclei and with pale blue protoplasm. The nuclei of the epithelioid cells occasionally show mitotic figures. There are some polymorphonuclear leucocytes and a great abundance of *eosinophiles* with granular protoplasm scattered rather evenly throughout the gland; no more numerous, however, at the periphery than in the center. These have nearly all trilobed nuclei, but occasionally one with a bilobed nucleus is seen, or a smaller cell with a small round nucleus. Certain areas contain particles of brownish pigment.

Another of the lymph glands (probably mesenteric), enlarged to about 3 cm. in length, shows a marked abundance of hyperplastic cells. The gland is divided about one third from one end by a septum of fibrous cells, while the capsule is a fairly thick fibrous structure. There are a few areas composed of lymphoid cells, also containing some polymorphonuclear leucocytes and plasma cells, a few giant cells and oval-shaped or epithelioid cells, and a few eosinophiles. Most of the gland shows, however, a diffuse hyperplasia of new formed cells in a network of fibrous tissue, which in places is quite abundant to the exclusion of other cells. These cells consist for the most part of various sized oval-shaped or epithelioid cells, generally of moderate size, of spindle cells, and frequent giant cells, usually with 3 or 4 nuclei and a pinker protoplasm than the others, but occasionally containing more nuclei sometimes arranged in a circle. There are also plasma cells and some leucocytes. The eosinophiles are not so

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numerous as in the other gland or in the lung, liver or spleen, or else take the stain poorly, which seems rather to be the case. In a few places, however, they are fairly numerous. There is one area of necrosis filling about one third of the field of the low power objective (Leitz No. 3).

The left pleural cavity was normal. The *right* contained about a pint of clear fluid.

The left lung weighed 860 gm. and showed a few scattered small, firm, white areas similar to those of the right.

The right lung weighed 560 gm. and showed peculiar areas scattered throughout of white to light brown indurated tissue, especially marked at the base behind, a cross-section of this being from 5 cm. to 8 cm. in diameter. Here it was somewhat firm, with muco-pus exuding from the bronchi. This tissue also extended up along the median side near the hilus, bordering on enlarged lymphatic glands.

Microscopical sections of this area show in paraffin mounts stained both by Unna's methylene blue and eosin, and by Wright's stain, normal lung tissue which in many places is filled with cells, sometimes becoming a solid mass of abnormal tissue. These cells consist of mononuclear cells of a round and oval shape, or epithelioid cells, with nuclei both small and medium sized, and frequently vesicular, and occasionally there is a spindle cell. At times they contain vacuoles. In places the background consists of fibrous and spindle cells. Throughout this new formed tissue there are scattered some polymorphonuclear neutrophiles, lymphoid and plasma cells, and there are many *eosinophiles*, in places quite abundant. Most of them are polymorphonuclear with a trilobed nucleus, and with granular protoplasm, while others have a round or oval

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nucleus at one end. These cells are in the new-formed tissue, and at times in the exudate contained in some of the bronchi, though often absent. Mitotic figures occasionally occur in the epithelioid cells. The blood vessels also contain a few eosinophiles. The alveoli and bronchioles, both those appearing normal and those whose walls are thickened and infiltrated, contain an exudate of blood, some endothelial cells, lymphoid cells, and polymorphonuclear neutrophiles, and, as above stated, at times eosinophiles. The lymphatics and capillaries are somewhat dilated. In places there is an apparent organization going on in the alveoli resembling an organizing pneumonia. This is co-ordinate with the Hodgkin's disease, but not a part of it. Some of the erythrocytes are stained pink, and others yellow. Several sections of this new-formed tissue were stained for tubercle bacilli, but none were found.

The liver was enlarged, weighing 1,700 gm. The appearance when fresh was mottled, due to the contrast of normal brown red areas against the interspersed abundant white areas of "pseudo-leukemic" tissue, which vary from the size of the head of a pin, or less, to ½ cm. in diameter. The surface was smooth and regular.

Microscopic sections stained by both Unna's and Wright's stain show the parenchyma with some cloudy swelling and considerable infiltration of the liver cells with fat, and some intercellular invasion of polymorphonuclear leucocytes. At the corners of the lobules are areas varying in size, generally round or polygonal in shape, near and surrounding the bile ducts and vessels, at times quite large, infiltrating irregularly and nearly replacing whole lobules. They correspond to the white areas of the gross. They contain connective tissue and a variety of hyperplastic cells, spindle cells,

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oval or epithelioid cells and medium sized mononuclear cells with a vesicular nucleus, a few of which have a pinkish protoplasm with Wright's stain, a few lymphoid cells, plasma cells, and a considerable number of polymorphonuclear neutrophiles. There are often collections of lymphoid cells, but no large areas of these. There is an occasional small-sized giant cell with the grouping of three or four nuclei in the center, and a bluish protoplasm. The epithelioid cells are occasionally undergoing mitosis. Some areas are more fibrous, some have more spindle cells, some have more of the other varieties, some have no ducts. Throughout the tissue are numerous *eosinophiles*, quite abundant, especially in the areas of new-formed atypical tissue, but also present among and invading the parenchyma. These are similar to those heretofore described. One on careful focusing gave the appearance of thrusting out a pseudopod. The central cells of the lobules contain an excess of blood pigment. Erythrocytes are scattered throughout, some staining pink, and others yellow.

Spleen: Slightly enlarged, weighing 270 gm., of normal red color, but giving the suggestion of the porphyry appearance from minute whitish areas. One such area is about one half a centimeter in diameter, oval in shape. Trabeculæ markings were normal. The capsule was normal, and the surface smooth.

Microscopical examination of sections, stained both by Unna's and by Wright's stain, show the trabeculæ normal. In places they contain spindle cells. A few small Malpighian bodies are present, containing lymphoid cells, a few leucocytes, an occasional spindle-shaped cell of medium size, an occasional red blood corpuscle, and frequently an abundant number of *eosinophiles*. Scattered throughout are several pale-

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staining areas somewhat larger than the Malpighian bodies. Sometimes these are fibrous in character, though containing a few each of the above-mentioned cells, but sometimes they are cellular, containing oval or epithelioid and spindle-shaped cells. The larger white area, mentioned above in the gross, contains a hyaline-like background, in which are scattered a few of the above-mentioned cells, excepting the eosinophiles, and a number of nuclei, especially of lymphoid cells and leucocytes. One area seems to contain chiefly these extruded nuclei.

The rest of the spleen pulp consists of a stroma infiltrated with atypical small and medium-sized, round and oval cells, with both small and vesicular nuclei which occasionally are dividing. There are also spindle cells, and an occasional giant cell with pink or bluish protoplasm and three to six nuclei. There are lymphoid cells, some polymorphonuclear leucocytes together with an abundance of eosinophiles, in places very thick. These stain somewhat better by Wright's method, though well by Unna's. These have generally a trilobed or horseshoe nucleus, often, however, small and solid, occasionally larger, and more vesicular. Rarely there is a larger form with nuclei in opposite sides, and occasionally the nucleus is protruding. Throughout are scattered erythrocytes in places in large masses, often staining a golden red color, or sometimes a yellow, while there are collections of blood pigment of a dirty yellow.

Kidneys: One weighed 140 gm.; the other 120. *Macroscopically*, the cortex was normal, and the kidney as a whole was rather pale. *Microscopically*, there is some cloudy swelling of the convoluted tubules, which as a rule contain a considerable amount of granular material. The glomerulæ show a slight increase of the

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nuclei, and occasionally a slight desquamation into the periglomerular space.

The stomach, intestines and appendix were normal. The intestines contained no evidence of parasites.

The diaphragm and muscles of the chest and abdominal cavity were smooth, and macroscopically gave no evidence of the presence of trichinæ.

Unfortunately, the *bone marrow* was not examined.

The pathology of Hodgkin's disease has been fairly definitely settled since the researches of Reed were published in 1902. Whatever the relation of Hodgkin's disease to leukemia, lymphosarcoma, sarcoma of lymph glands, and tuberculosis, if there is any one pathological condition that is a type of the disease, then aside from the general eosinophilia the case now reported corresponds to that type.

Hodgkin's disease is characterized by a hyperplasia of lymphoid tissue, the cells, many of which probably originate from the reticulum, consisting of many varieties of epithelioid, spindle, lymphoid and plasma cells, eosinophiles, fibrous cells, in any lymphoid structure of the body, notably the lymph glands, liver and spleen, the latter acquiring the so-called " red-porphyry " appearance. Pinkus [1] states that the lymph glands show the normal arrangement with a proliferating center of large cells and a peripheral layer of small cells, the histological picture corresponding exactly to that of lymphatic leukemia. Other authors,[2] however, give a different and more specific pathology.

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Dorothy Reed [8] says: "In the smallest gland examined . . . we found only proliferation of the flat so-called endothelial cells, which cover the reticulum of the lymph sinuses, and of the large cells of the centers of the lymph nodes which are presumably identical cells. Mitotic figures in cells of this description are frequently seen. . . . As the process advances we find the lymph spaces filled with masses of lymphocytes and proliferating endothelial cells. The presence of these newly formed cellular elements destroys the normal appearance of the gland. . . . The endothelial cells, which show many karyokinetic figures, in proliferating form large epithelioid cells with vesicular nuclei. Numerous giant cells with one or more nuclei and prominent nucleoli appear in great numbers. . . . Occasionally a very large giant cell with many small nuclei peripherally arranged is seen. . . . The lymphoid cells . . . are of the usual small type. . . . Plasma cells are often observed in almost as great numbers as the lymphocytes. Eosinophiles are usually abundant throughout the tissue spaces, except in the germinal centers of the follicles. . . . As the process advances the connective tissue shows marked proliferation. The framework of the gland becomes increased and bands of connective tissue, starting often from about the vessels, gradually break up the gland substance into coarse lobules . . . at the expense of the other cells. . . . The capsule of the gland usually shows no change, except possibly some thickening."

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Eosinophiles were first observed in a case of Hodgkin's disease or malignant lymphoma in the lymph glands by Goldmann [4] in 1892. Since then they have been observed by other writers,[5] and although they were thought to have a certain diagnostic value, still they are not characteristic since they are found occasionally in other varieties of lymphomata, and they are by no means constant in Hodgkin's disease.[6] In several cases of Hodgkin's disease they have been, however, very numerous.

A case of Hodgkin's disease where the eosinophiles have invaded the liver, spleen, lung and lymph glands in such large numbers and occurring in the blood to such an extent, namely, 68.2% or 33,418 per cubic millimeter in a total leucocytosis of 49,000, I have been unable to find reported. Dreschfeld,[7] in 1892, stated that eosinophiles were present in fairly large quantities in the blood in some cases, but specified no examples.

Cabot, in 1897, cited one case [8] with 9.3% eosinophiles, the white count not being increased, and in 1898 cited another [9] with 7%, or 826 eosinophiles in a leucocytosis of 11,800.

Einhorn,[10] in 1902, reported a case with 10% eosinophiles or 730 per cubic millimeter in a white count of 7,300. Later there were 12.4%. Longcope,[11] in 1903, reported a case with 2.8% eosinophiles or 563 in a leucocytosis of 20,100, in which later the percentage fell to 2.4%, but the absolute number rose to 1,872 in a white count of 78,000.

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They were numerous in the glands, and increased in the bone marrow.

Longcope,[12] in 1906, reported a case showing 13.2% or 1,491 eosinophiles per cubic millimeter with a total leucocytosis of 11,300, a few large mononuclear eosinophiles in the thymus, but only a few were noted in the spleen and in the lungs; none were seen in the liver; and there was an increase of eosinophilic myelocytes in the bone marrow.

Pepper [13] has recently reported a case with 16% of eosinophiles, or 4,608 in a total white count of 28,800; enormous numbers of eosinophiles were found in an excised axillary gland. He also mentioned two other cases at the Pennsylvania Hospital, with 8.8% and 10.6%, respectively, of eosinophiles in the blood. Of twenty cases of Hodgkin's disease he found 20% had eosinophilia.

Nowack,[14] in 1905, reported a case with 24.5% eosinophiles per cubic millimeter, or 940 per cubic millimeter in a white count of 3,840.

Several other cases [15] have also been reported, showing a slight absolute increase of eosinophiles in the blood, varying from 250 or 300 per cubic millimeter (the upper limits of normal)[16] to 1,173 and up to 5% (the normal being 1% to 4%),[16] but in the organs they were numerous only in the lymph glands, except one case [17] with 4.4% eosinophiles or 550 in a white count of 12,500, with abundant eosinophiles in the lymph glands and spleen, and a few in the liver and lung.

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Another case [18] showed eosinophiles in the spleen and liver, while they were numerous in the lymph glands. In the blood, however, there were only 272 per cubic millimeter. A few other cases [19] showed a few eosinophiles in the spleen or liver, but no large excess in the blood. On the other hand, in a case of lymphosarcoma colli [20] 60,000 eosinophiles per cubic millimeter have been found.

The small relative number of lymphocytes in this case (3.8%–6%) is consistent with a diagnosis of Hodgkin's disease. Notwithstanding that it has been asserted that in Hodgkin's disease there is a relative lymphocytosis,[21] this statement is disputed,[22] and there is sufficient evidence to show that in a certain proportion of cases there is a normal or low number of lymphocytes.[23] That the proliferation in the lung is not evidence of a sarcoma is supported by two cases of Hodgkin's disease reported by MacCallum,[24] in one of which the disease invaded the right lung, and in the other, both lungs. Apparently, Hodgkin's disease is a hyperplasia of pre-existing lymphoid tissue, anywhere in the body, rather than an infiltration or transplantation of new growth cells.[25] Pseudo-leukemia gastro-intestinalis, a recognized type of disease, is an example of this.[26]

The presence of dyspnea in the case under discussion possibly may be considered evidence of asthma, and as such a sufficient cause for the excessive eosinophilia. But it is not so likely that this was the cause of the eosinophilia, as

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that the hyperplasia and changes in the lung were the cause of the dyspnea. Further, I am not aware that asthma causes a marked presence of eosinophiles in the various internal organs. In a pure asthma the total white count is only slightly raised, if at all, and when bronchitis is present the count runs from 6,000 up to 26,000,[27] although one case showed 45,000,[28] running up to 68,000 before death. The maximum percentage of eosinophiles in asthma reported is 53.6%,[29] but their absolute number was only 4,449 per cubic millimeter in a white count of 8,300, while another case showed 25% or 13,000, in a white count of 52,000,[30] but still considerably below the percentage and absolute number in the present case. Also our case had had no recent attack of dyspnea at the time of entrance, and it was not till two days later that there was any suggestion of an asthmatic attack, and then, instead of the percentage of eosinophiles rising, they fell from 68.2% to 60.8% with a falling white count. So the most we can say is that if there was any true asthma present in our case (which is extremely doubtful) its influence on the production of eosinophiles was only slight, partial and contributory with other causes inherent to the Hodgkin's disease.

Being of so marked a type, and differing so from the usual run of Hodgkin's disease, and unless recognized as a type so likely to lead to confusion in diagnosis, the present case is worthy of the descriptive title, *Pseudo-leukemia Eosinophilica.*

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The origin of these eosinophiles is held by Opie [31] to be the bone marrow, although others maintain they are formed locally in various affections. As Longcope [32] says, in Hodgkin's disease, " We can only suppose they accumulate in the tumor nodules by one of two methods. On the one hand, it is possible that they are formed locally in the lymphomatous tumors; on the other hand, they are brought to this situation by the blood stream." Goldmann [33] and Dorothy Reed [34] held this latter view. In our own case the preponderance of eosinophiles in the blood would favor also this view. We have, in all likelihood, what is probably an exaggerated type of the frequent occurrence of eosinophiles in Hodgkin's disease, and not a blood disease *sui generis*, carried a degree further than Longcope's, Nowack's and Pepper's cases to an eosinophilia of many of the organs.

In conclusion, I wish to express my thanks for advice and assistance to Drs. Henry A. Christian, Frederick H. Baker and Ernest L. Hunt, and to Miss Ora M. Mills.

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SAHLI'S BUTYROMETRIC TEST OF GASTRIC FUNCTION.*

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IN 1902 a method of stomach examination was published by Sahli,[1] of Berne, and by Seiler,[2] his assistant, which from its ingenuity of conception and its theoretical advantages promised much. A few articles, however, soon appeared which questioned the reliability of the test, and also criticised it as too complicated for practical use; but articles dealing with the subject have been too few to lead to definite conclusions. Since the method must continue to attract attention as appearing in Sahli's valuable book upon diagnostic methods,[3] and since in its author's hands it is reported in later communications as still being used with satisfactory results, a further consideration is desirable.

In principle the test is a development from the earlier attempts, notably those of von Mering and of Strauss, to measure the activities of the stomach by introducing into it with a test diet some substance not acted upon by the stomach which in subsequent tests of the stomach contents might serve as an index of the amount of the test

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diet still remaining. Sahli's test is also performed with more stress upon quantitative determinations of amounts, given and withdrawn, than are the older tests. The following advantages are claimed for it: (1) In addition to determining the simple acidity of the mixed contents it is possible to determine the composition, by showing to what extent the specimen is composed of the substance ingested, and to what extent it is composed of gastric juice. (2) The amount and the acidity of the pure gastric juice can be determined; thus one can distinguish between hyperacidity and gastrosuccorrhea, and between subacidity with secretion normal in amount and subacidity due to diminished secretion. (3) Numerical values may be obtained indicating the degree of gastric motility; this may be of value in determining the degree of stasis in cases of pyloric stenosis and in showing variations resulting from medical or from surgical treatment. (4) All data to be obtained by means of the Ewald breakfast are said to be obtained as well by this method. (5) The process is not disagreeable to the patient. The soup employed as a test meal is not distasteful, and by reason of its fluid consistency it can be easily and rapidly withdrawn.

The theoretical basis of the test deserves careful study. The test soup, of which 300 ccm. are given, is esentially a stable fat emulsion, a sample of which is kept for comparison with what is later obtained from the stomach. The fat percentage is determined, 1st, in the original soup,

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and, 2d, in the stomach contents obtained an hour after ingestion. In normal cases the fat percentage in the stomach contents is found to be only about a half as great as that of the original emulsion. Now since fat cannot be absorbed from the stomach this fall in the fat percentage must be due to *dilution* of the fluid ingested *by gastric secretion.* The relative fat percentages measure this dilution since excessive secretion obviously causes excessive dilution, and lessened secretion causes a less degree of dilution. Thus, in the contents obtained, it can be learned how much is soup and how much is secretion. The proportion of secretion in the contents thus being known and the acidity of the total contents being easily determined by the usual titration, the acidity of the pure gastric juice can be calculated. To obtain an index of motility the amount of contents is measured, and the extent to which this is composed of the original soup is calculated from its fat percentage. The relation which the amount of soup residue bears to the amount of soup ingested indicates what proportion of the test emulsion still remains in the stomach at the end of an hour, and what proportion has passed on beyond the pylorus.

The test is performed as follows: A soup is prepared by heating 15 gm. of butter and 25 gm. of flour in a pan with constant stirring until the mixture becomes browned to the color of strong coffee with milk. To this are added slowly 350 ccm. of hot water and the whole is boiled for five

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minutes, after which water is added up to the original 350 ccm., and also 3.5 gm. (1%) of salt. This soup is fairly agreeable in taste and is a stable emulsion of the butter fat, without tendency to separate in layers of different concentration.

Of this soup, still hot, the patient is given 300 ccm. to be eaten with a spoon. The remaining 50 ccm. are kept for subsequent fat estimation. The patient's stomach should be washed clean before the soup is given.

After an hour the stomach contents are withdrawn as completely as possibly, and then 300 ccm. of warm water are allowed to run in and out, several times, to determine the amount of residue after the method of Matthieu,[4] as will be described later.

The stomach contents obtained should present the appearance of a perfect emulsion without visible fat globules.

Three specimens are then at hand which are, the materials for laboratory study,—the original soup, the stomach contents and the washings with the 300 ccm. of water. The ordinary chemical tests of the contents are first performed as with the contents after the Ewald breakfast. Free HCl † and total acidity are determined quantitatively. The lactic acid and the guaiac or benzidin tests or any other tests usually tried may

† Töpfer's agent is rapidly decomposed when added to this fat-containing material. In quantitating the free HCl, therefore, successive drops of Töpfer's solution on a porcelain plate, or filter paper saturated with Töpfer's solution, are touched at intervals during the titration with a glass stirring rod dipped in the contents, as the NaOH solution is run in.

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be made, but are not an essential part of this method. The washings with the 300 ccm. of water are next tested for total acidity. From this we are in the position to apply the formula for estimating the amount remaining in the stomach after no more pure contents can be withdrawn through the tube:

$$\frac{x=300\times b}{a-b},$$

x being the amount of residue in centimeters; 300 ccm., the amount of wash water; b, the acidity of the washings; and a the acidity of the undiluted contents.

The result of this calculation added to the actual amount of contents is the total amount contained in the stomach at the conclusion of the test.

Thus the amount contained in the stomach being known, its composition, and the relative amounts in it of gastric secretion and of test soup are to be estimated. To this end the fat percentage of the original soup (F) and of the stomach contents (f) are determined. Sahli and Seiler recommend a modification of Gerber's butyrometric method. The author has found that the small tubes sold in this country for testing milk by the Babcock process are sufficiently accurate for purposes of the test. These are filled with 5 ccm. of the contents or of the fat emulsion, to which is added 1 ccm. of amyl alcohol and then concentrated sulphuric acid up to the shoulder of the tube. Shreds of mucus are first to be removed by forceps. Both tubes so filled are then mixed by rotation and then centrifuged for five minutes. The tubes are then allowed to stand

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upright in hot water for a few minutes, after which hot water is introduced until the surface of their contents reaches the zero point of the graduations. After a second centrifugalization of one minute the results are read off. It is necessary to work rapidly to prevent cooling and contraction in the bulbs.

The reading ("*f*"), the percentage of fat in the stomach contents, divided by ("*F*"), the percentage of fat in the original soup, indicates the proportion in which the stomach contents are composed of soup ingested. In normal cases the value (*f*) is found to be approximately half as great as (*F*), showing that the contents are made up of nearly equal parts of soup ingested and of secretion. To obtain absolute amounts of soup and of secretion the amount of the total contents (including the estimated residue) is multiplied by $\frac{f}{F}$; the result is the number of cubic centimeters of the test soup remaining in the stomach at the end of the hour. The difference between this amount and the total contents is the amount of secretion. To obtain the acidity of the pure secretion the acidity of the mixed contents is multiplied by $\frac{F}{f}$. Normally, according to Seiler, this is from .35% to .44%.

The amount of test emulsion remaining in the stomach at the end of the hour being known, the difference between this and the original 300 ccm. must have passed through the pylorus to the intestines. In normal cases, it is said, the total residue should not be over 160 ccm., the amounts

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of secretion and of soup residue varying between 30 ccm. and 80 ccm. The amount of the test fluid passing through the pylorus within the hour should be from 75% to 90%.

A few illustrative cases may serve to show the significance of the results obtained.

Case I. A man aged twenty-eight, a shoe-worker, had complained for five months of poor appetite, eructations and acid regurgitation, pyrosis, pain worse an hour after meals, and occasional nausea. He was neurotic and overworked, but had not lost weight. By the method described above the following values were obtained. Total residue 65 ccm., a low amount, suggesting high motility. In this free HCl was present to .10% and the total acidity amounted to .146%. The fat percentage of the original emulsion (*F*) was found to be 1.8% and that of the stomach contents (*f*) was .8%. From this it follows that the total residue of 65 ccm. was made up of 36 ccm. of secretion and of 29 ccm. of the original soup. The acidity of the contents being .146, the acidity of the pure secretion must be .26%.‡ The soup residue of but 29 ccm. shows that over 90% of the test fluid has passed through the pylorus within an hour. These results show no notable abnormality of function but suggest the presence of a hypermotility such as is often present as a part of a gastric neurosis. (See also Case XIII in table.)

Case XVIII. A man aged forty-three had com-

‡In this case the directions of Sahli, who uses the total acidity as the basis for his calculations of the acidity of the gastric juice, were followed. Except in earlier determinations, however, the author has based this calculation upon determinations of the total HCl by Congo red, or by the alizarin method, so as to leave out of account the slight acidity of the soup itself. The acidity values are thereby somewhat lowered, but must be nearer to the truth.

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plained for ten months of distress beginning immediately after meals, with pyrosis and belching of wind, gradually increasing. For six weeks before entering the hospital he had had attacks of vomiting about once in three days, after which he would feel better for a day. The vomitus was, as a rule, large in amount, watery and sour, thought not to contain food, but containing a dark-brown sediment. The man had lost 55 lb. in six months. The fasting contents on the day after entrance were 630 ccm., slightly turbid, with slight brownish sediment, few starch granules and fat drops, free HCl .22%, total acid .24%, lactic acid absent, guaiac test positive. Daily lavage showed similar contents of the fasting stomach although the amount gradually diminished. Seventeen days after entrance the amount of fasting contents was 240 ccm. Sahli test performed on this day resulted as follows, Total residue 420 ccm.; Free HCl, .146%; total acidity, .22%; secretion, 327 ccm.; of acidity, .28%. Soup residue, 93 ccm. Per cent passed out of the stomach in an hour, 69%. The high relative amount of secretion shows strikingly the condition of hypersecretion or gastrosuccorrhea. (Absence of pyloric stricture is probable from the complete disappearance of gastric symptoms during the next year.)

Case XXI. A man aged forty-five, who for two years had complained of gradually increasing sense of fullness in the stomach, with eructations and regurgitation, showing an emaciated condition, with visible gastric peristalsis, was found by this test to have a total contents of 454 ccm., calculations from which showed that *only* 16% of the test emulsion had passed the pylorus. Operation by Dr. M. H. Richardson revealed a ring-like cancer at the pylorus which was removed by pylorectomy. Three weeks after the operation the

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Number.	Date.	Fasting contents, amount in ccm.	Food remains.	Micro-organisms.
1	Aug. 30 ...	20	0	0
2	Aug. 30 ...	0	0	0
3	Aug. 5	—	—	—
„	Aug. 17 ...	0	0	0
„	Sept. 22...	630	+	—
4	Sept. 1....	5	0	0
„	Sept. 13...	0	0	—
5	Sept. 11...	190	Sl.	yeast
6	Aug. 10 ..	0	0	—
„	Aug. 18 ...	20	0	0
7	Aug. 25 ...	0	0	0
„	Sept. 5....	—	—	—
8	Aug. 25 ...	30	0	0
9	Sept. 14...	0	0	—
10	Sept. 18...	3	0	—
11	Sept. 25...	5	0	—
12	Sept. 28...	0	0	—
13	Oct. 7.....	*	*	*
14	Oct. 7.....	0	0	—
15	Oct. 9.....	2	0	—
16	Oct. 12....	0	—	—
17	Oct. 23....	0	0	—
„	Nov. 6	—	—	—
18	Nov. 16 ...	630	Sl.	sarcin
„	Dec. 3	240	—	—
19	Oct. 30....	10	0	0
„	Jan. 27....	—	—	—
20	Aug. 1	25	0	yeast
21	Aug. 22 ...	275	+	sarcin
„	Aug. 23 ...	250	+	sarcin
„	Sept. 18...	140	+	0
22	Nov. 8	0	—	—
23	Oct. 28....	10	0	0
24	Nov. 9	10	0	0
26	Nov. 16 ...	30	0	0
27	Dec. 2.....	10	0	sarcin
28	Nov. 29...	68	0	0
„	Dec. 12 ...	60	0	—
„	Feb. 1	—	—	—
29	Oct. 9.....	40	—	—
30	Dec. 14....	10	—	—
31	Jan. 2.....	—	—	—
32	Dec. 28 ...	175	+	sarcin
33	Jan. 6.....	90	+	—
34	Jan. 6.....	15	—	—
35	April 1....	350	+	—
36	Feb. 2	10	0	—
37	July 11....	0	Sl.	0
„	July 12....	+	—	—
	July 13	+	—	—

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gastrica tested by this method in which secretion was present. It was unfortunately impossible to repeat the test.

In one case only (Case XXXVI) have I obtained a result such as Koziczkowsky obtained in several cases, showing complete proof that in this case the method was at fault. The patient, a woman aged fifty-six, complaining of gas in stomach and distress after eating, relieved by belching, was found to have, one hour after ingestion of 300 ccm. of the test soup, contents containing a percentage of fat higher than that of the original soup ingested. If we exclude the possibility of absorption of water through the stomach walls, shown by Senator not to occur, this result can be explained only by the assumption that the contents in the stomach separated into two layers, the upper one becoming richer in fat and the lower one only passing through the pylorus. The emulsion of fat in the contents, however, was not broken up; unlike the contents in 8 cases excluded from this series as obviously failures of technic it contained no macroscopic fat drops. The existence of gastric stasis was excluded by the absence of residue in the fasting stomach and by the fact that dried currants given by mouth appeared normally in the dejections.

The results of other authors as to the value of this method may be summarized as follows: Koziczkowsky,[5] in Senator's clinic, made tests to determine whether the test emulsions remain homogeneously distributed in the stomach.

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hour. This variation obviously cannot be brought forward as evidence against the method.

I have unfortunately few cases where tests were repeated without change of conditions. Case III, from Aug. 5 to Sept. 22, presents the development of a pyloric stenosis. Case XXI, between Aug. 23 and Sept. 18, had undergone pylorectomy. In cases XXXVII and XXXVIII, although conditions seemed the same on the different days, still great variations occurred in the amounts of fasting contents and of contents at the end of the test.

It must be understood that the method, like many clinical methods, cannot lay claim to such accuracy as is required by the analytical chemist. I freely admit that the error in my fat determinations may be 0.1% in either direction, perhaps sometimes even 0.2%, which is enough to influence considerably the calculated results. Yet I feel that in cases such as Case XXXVIII the three results, roughly similar, it is true, but yet widely different, are to be explained largely by irregular action of the stomach.

Finally, as to the question of the homogeneity of the stomach contents, the question according to the decision of which the test must stand or fall: In one case (Case XXXVI), perhaps also in another (Case XXII), we have evidence agreeing with that of Koziczkowsky and of Bonniger, that separation of fat from its suspending fluid has occurred. Case XXXV may also be suspected of showing a similar process by which the fat containing portion has been the first to pass out of the stomach. I am also able to agree with Zweig

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and Calvo that in certain cases, in spite of every precaution, the emulsion of fat may be broken up in the stomach so that the fat is found floating in large drops at the surface of the stomach contents. Such conditions obviously show that in these cases the test has failed. Yet I can also prove that this method is not always open to such objections. In Case XXXVIII, on Feb. 16, the contents were drawn by Koziczkowsky's method from two levels. In the first, the upper layer, the readings were as follows: (1) 1.0%, (2) 0.9+%. In the second layer (the larger) the readings were: (1) 0.8+%, (2) 0.9%. On Feb. 19 the contents were withdrawn in three layers which contained the following percentages: 1st layer, 1.1%, 2d layer, 1.2%, 3d layer, 1.0%. In testing a few of my earlier cases, observations as to this same question were made. Although I have unfortunately mislaid the readings they showed no such great variations as those of Koziczkowsky and Bonniger. Moreover, if the glaring errors found by Koziczkowsky are of frequent occurrence, it is strange that more inconsistencies have not become evident in the course of the series of cases recorded in my table.

The question naturally arises, how we are to distinguish cases in which the results are reliable from those in which they are fallacious. Sahli has answered this by advising that in every case the contents be withdrawn in two portions so as to detect undue variation. This adds to the time required by the test, but I feel that it is the only solution of the difficulty possible if we are to con-

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tinue to use this test fluid which we must admit is liable in some cases to separation.

Thus we have in this method a procedure which, in spite of a liability in some cases to complete failure, offers in other cases, at the price of an hour's extra work, information, probably at least roughly accurate, of a nature which we cannot otherwise obtain. It must be admitted that the method lacks much of being an ideal application of the theoretical considerations upon which it is based. It is strongly to be hoped that better solutions of the problem which this method attempts may be brought forth.

But the final question to be considered is whether this method as it stands is to be accepted with its limitations or whether it is to be entirely discarded. Personally I feel that for certain cases, especially where there is question of impaired motility or of hypersecretion, and where circumstances demand that every effort shall be made to arrive at a diagnosis, this method is not without value.

In conclusion I beg leave to express my gratitude to Dr. Maurice H. Richardson and to the physicians of the Massachusetts General Hospital for clinical opportunities, without which this work could not have been done.

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Feb. 25. Test breakfast. Reaction neutral. Pepsin and rennin present. Schmidt's test for bile in stool positive.

Feb. 28. Discharged. Diarrhea less marked during last few days. Still some epigastric distention.

Analysis of Stool Passed Dec. 18, 1903.

	Composition of fecal fat.
Nitrogen, 3.3%	Neutral fat, 11%
Fat, 62.7%	Fatty acids, 23%
	Soaps, 66%

Case II. W. S., age, forty-eight years. Single, born in New York. Overseer of orange plantation in Porto Rico for the past fifteen years. Entered Dr. Fitz's service, Massachusetts General Hospital Nov. 1, 1905.

F. H. Father living and well. Mother, one brother, and an aunt died of consumption. One sister living who has consumption.

P. H. Mumps in childhood. Intermittent fever in 1890, followed three months later by "typhoid malaria." Malarial fever in 1894. Denies lues.

Habits: Tea and coffee in moderation. No alcohol or tobacco.

P. I. For the last two years he has felt "run down" and has been unable to do as much work as formerly and gets easily fatigued. For the last year has occasionally had loose movements of the bowels for a few days at a time, but in the intervals stools have been formed and have averaged one a day. Two months ago he began to have diarrhea which has persisted ever since. The movements are of the consistency of paste, sometimes watery, never formed; frequency, two to three a day. Color light yellow. Patient says they frequently contain mucus, but never any blood. They sometimes have foul odor, but as a rule the odor has not been re-

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markable. Slight abdominal pain on defecation, but aside from this he has no pain. Appetite poor. Has vomited twice in the last month, once after taking porter, once after chocolate. Noticed nothing remarkable about the vomitus. Has lost flesh. Usual weight 125 lb., now 115 lb. Has never been jaundiced. No cough, dyspnea, or urinary symptoms. He left his work in Porto Rico two weeks ago, coming directly to Boston.

P. E. Well developed. Poorly nourished. Skin sallow. Over buttocks and inner aspect of thighs is an area of dark-brown pigmentation, which shows a tendency to scale, especially in the central portion. Conjunctivæ normal. Teeth poor. Throat negative. A few glands in groins, axillæ and neck the size of a pea. Lungs: Slight dullness in left supraclavicular fossa, and dullness at left base behind. Heart: Area of cardiac dullness not enlarged. Action regular and of good quality. Abdomen: Level, soft, tympanitic. No shifting dullness. No masses or tenderness. Liver: Upper limit of dullness in right mammillary line at fourth rib, flatness fifth rib. Lower border at costal margin; edge not felt. Spleen enlarged to percussion; edge not felt. Genitals normal. No edema of extremities. Knee jerks present and equal. Rectal examination negative. Prostate of normal size. No masses or tenderness. Temperature, pulse and respiration normal at entrance and remained so throughout entire stay in hospital of fourteen weeks. Weight, 102 lb. on Nov. 6. At time of discharge weight had fallen to 97 lb.

Blood: Hemoglobin 80%; leucocytes 4,800; erythrocytes 3,500,000. Stained specimen showed only a relative increase in polynuclear neutrophiles (82%).

Urine: Faint trace of albumin found repeatedly,

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but never any casts. Bile was present at first examination, but not afterward.

Stool: light clay color, semisolid, no froth or mucus, odor not abnormal. Microscopical examination: No blood, pus, amebæ, or parasites. Rare ovum of Tricocephalus dispar. Guaiac test for blood negative. No tubercle bacilli present.

Patient remained under observation for fourteen weeks during which time his symptoms varied but little. Lassitude, weakness, anorexia and diarrhea were the chief complaints, occasionally nausea, rarely vomiting. The abdomen was frequently distended by gas. Pain was either absent or slight and occurred chiefly in association with abdominal distention. Movements varied from one to ten daily. The number was little influenced by treatment. Average number of stools two to four daily. Pancreatin was given without effect. The stools were examined daily. They were always bulky, semisolid, never formed, light yellow or clay colored, often noticeably frothy and of normal odor. The most constant microscopic finding was large quantities of fat occurring as drops and crystals. At times stools were seen which showed yellow streaks of practically pure fat. Muscle fibers were frequently seen, but not in large numbers and not constantly. A diet poor in meat was given. No mucus, except in December, when he was having six to ten movements daily. Occasionally the guaiac test for blood was positive; no blood was ever seen macroscopically or microscopically. The eggs of Tricocephalus dispar were sometimes found. For several days during December sarcinæ were present in large numbers. Starch granules were found in some stools. Discharged Feb. 6, 1906, slightly relieved.

Subsequent history: On leaving the hospital on Feb. 6 patient went to Syracuse, N. Y., where he

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gained 4 lb. in five days. On Feb. 11, while at dinner table he suddenly vomited blood, and later in the day again vomited and also passed blood by rectum. On Feb. 13, again had hemorrhages from stomach and bowels, and on Feb. 14, further hemorrhage from bowels. At the date of writing (March 7, 1906), there was no pain and he was steadily improving. Diarrhea had ceased and he was having one formed movement a day.

Analysis of Clay Colored Stool.

		Composition of fecal fat.	
Nitrogen,	3.2%	Neutral fat,	24.3%
Fat,	53%	Fatty acids,	19.1%
		Soaps,	56.6%

Commentary.—The most interesting feature in these two cases of chronic diarrhea is the fatty character of the stools. In Case I, 62.7% of the dried stool was composed of fat, and in Case II, 53%. Normally the stools contain less than 30% of fat, except in rare instances with a diet unusually rich in fat. In pancreatic disease without icterus the percentage of fat, as Brugsch has pointed out, is rarely more than 55%. As the stools were bulky and numerous in both our cases the total amount of fat not utilized by the body must have been large.

In the following table the results of our analyses of the fecal fats and those obtained in health are compared:

	Percentage of fat in dried stool.	Neutral fat.	Fatty acids.	Soaps.
Health, milk diet,[5]	21	27.8	51.3	20.9
,, ,, ,,[5]		20.5	39.8	40.5
,, bread and milk,[5]		24.8	25.3	49.7
Case I. B. D.,	62.7	11	23	66
Case II. W. D. S.,	53.0	24.3	19.1	56.6

[5] Müller: Zeitschr. für klin. Med., 1887, xii, p. 45.

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It will be seen from this table that in our two cases the proportions of neutral fat, fatty acids and soaps correspond closely to those obtained in health. In the stool from Case I there was more splitting of the fat than is usual even in health. The analyses do not indicate any lessening of pancreatic digestion.

Aside from the fact that the stools are fatty there is no evidence in these cases that the disease is pancreatic in origin. A. Schmidt has recently described under the term "pancreatic achylia," cases that bear a superficial clinical resemblance to the two here reported. His patients suffered from diarrhea of long standing. There was considerable distention of the abdomen at times. The stools were frothy and contained considerable fat. Microscopic examination showed that the fat occurred chiefly in the form of droplets (neutral fat). The stools showed considerable starch. Sahli's glutoid test of pancreatic function was negative in one of his cases while it was positive in one of ours, thus supporting the view that the form of fatty diarrhea he was studying was of pancreatic origin, while the disturbance in the absorption of the fat in our cases was not of pancreatic origin. Unfortunately, Schmidt made no chemical analysis of the composition of the fecal fat so that the proportion of split fat is unknown. The nucleus or meat bag test of pancreatic disease which Schmidt has devised was negative in his cases. It is to be regretted that this test was not used by us. The percentage of fat was larger in our cases than in those of

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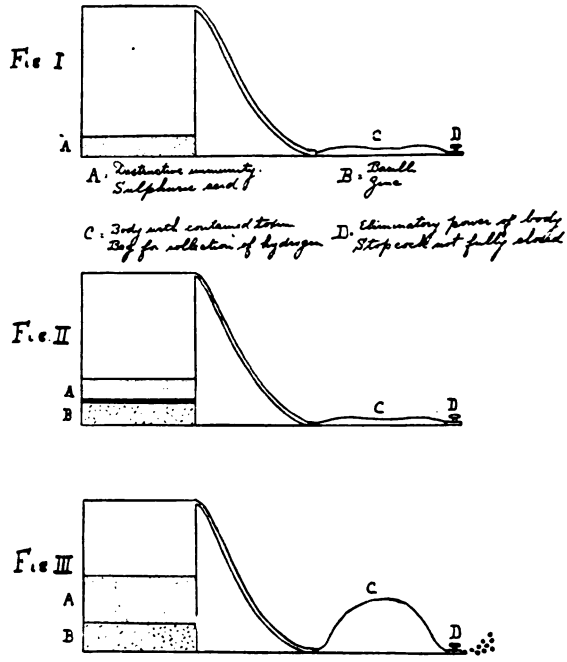
large number of typhoid bacilli, a rapidly increasing and energetically acting immunity might be actually inimical to its own proper purpose, and destructive to life, because it set free too much intracellular poison within too short a space



of time. In fact this has seemed to me a probable explanation of the fulminating type of typhoid, and, possibly, of other bacterial diseases. The immunizing apparatus once aroused, acts *too* well for the good of the individual. The powers of

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elimination, through skin, lungs, urine and feces, are limited, and excessive toxin production means rapid accumulation within the body. (See Fig. 5.) If, however, with the same power of elimination, this toxin production be spread out, let us say, over a period of three weeks instead of one, then the toxic condition will be comparatively mild and not dangerous, perhaps, to life. Finally in Figure 6 we have pictured the bodily condition after the disease process is over. There is, then, a large store of specific acquired immunity, sufficient, except in rare instances, to prevent any reinfection.

These points have an important bearing on the question of specific therapy, for, in the absence of a true antitoxin for the typhoid poison, we have been more and more tempted to introduce into the diseased body substances which should stimulate an increased destruction of the bacilli. This procedure is justified in cases not already very severely poisoned. In the cases, however, already hyper-intoxicated, the indication may well be, not to increase the rate of destruction of the bacilli, but, if possible, in some way, to hold it up. The blood serum of persons who die of typhoid is strongly protective in animal experiment. The opsonic index of persons moribund with the disease, I have found to be high. They do not die, apparently, because of a lack of protective substances. Do they not, some of them at least, die because their destructive power, as evidenced by their blood condition is *too* high?

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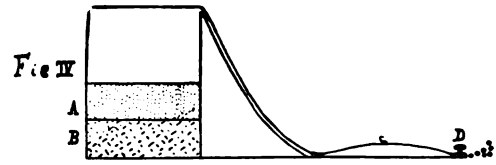
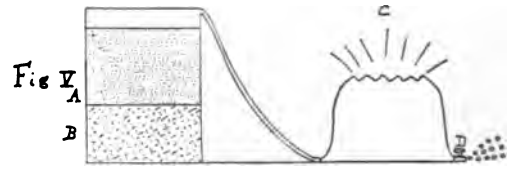
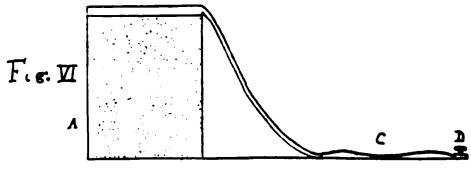
In the treatment of a series of cases with the non-toxic residue of the typhoid bacillus as prepared by Professor Vaughan of Ann Arbor,[1] it seemed to me that the cases were longer but milder than the ordinary run of cases. If this was true, was







it not due to the fact that this non-toxic residue of the typhoid germ, with its specific affinity for typhoid antibodies, diverted the destructive substances from the living, toxin-laden bacilli,

[1] On the treatment of typhoid fever with specific sera, filtrates and residues (Vaughan). Boston Med. and Surg. Jour., Oct. 3, 1907.

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and thus made the process longer but less severe? Furthermore, cannot this idea be used as a possible explanation of the beneficial effects of cold baths in typhoid fever? The destruction of the invading germ, whether it be through bacteriolysis or phagocytosis, is accomplished largely through digestive ferments, whose action becomes much impaired in the presence of low temperatures. The cold bath, then, inhibits the action of the destructive ferments over the large expanse of skin, and toxin production is thus decreased. The temperature drops, the patient feels better, and the tissues have a few hours' respite from hyper-intoxication.

For the same reason the exhibition of drugs calculated to lower cellular activity might well be indicated. Quinine is such a drug. Its use in large doses in pneumonia has been recommended and might be justified by this reasoning.

As long as there is bacillary destruction, so long will there be evidence of intoxication. It is said that bacilli have been cultivated from the blood a certain time after the cessation of symptoms. This phenomenon must be rare, but goes to prove my contention, that the typhoid organism causes little trouble till it is dead and disintegrated.

This picture of the essential nature of the disease makes a number of phenomena observed in typhoid fever more readily comprehensible. Take, for instance, the chill, which, though in general rare, in individual cases may be very

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common. According to my theory this represents a *sudden* destruction of bacilli as contrasted with the more evenly distributed production of toxin seen under ordinary circumstances. Thus the cases with sudden onset are apt to begin with a chill, their course is commonly unusually severe and their mortality is high. As stated above, it seems very probable that, in these instances, the protective substances act *too* well, and the individual is overwhelmed with toxin as a result of his excessive zeal in destruction.

In the treatment of typhoid patients with filtrates of living bouillon cultures (*loc. cit.*), chills were very common, and due, in my opinion, to sudden stimulation of the protective apparatus. Following the chill there occurred frequently a marked fall in temperature. This, to my mind, means that a period of over-stimulation was followed by a resting stage, and that, in the absence of toxin production, the temperature had to fall.

The same explanation would hold for those curious drops in temperature which, with no apparent cause, occur in typhoid fever, under routine forms of treatment. The intercurrent relapse may represent not a variation in the intensity of the infection, but a variation of the powers of resistance. Indeed, in the cases of true relapse, it is very possible that during the afebrile period, the bacilli are still there, perhaps increasing in numbers in the absence of resistance. Only when the body takes up again the work of

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destruction do symptoms appear. The fact that many cases which relapse retain their enlarged spleen would bear out further the idea that bacilli have persisted.

Further, I think the characteristic temperature curve of typhoid is susceptible of explanation by the use of our theory. In the beginning we have the step-like rise in the fever, inasmuch as more endotoxin is set free than can be eliminated. It collects, therefore, in the body, the degree of intoxication receding slightly each morning only to go still higher as the result of that day's destructive activities. Having reached a high level, the intoxication is so intense that the comparatively small amount excreted has no appreciable effect upon the general condition. In the later weeks, however, when there are comparatively few bacilli in the body, then, although the daily toxin production is sufficient to carry the temperature up to a high figure, the degree of intoxication is really small, and is more than counterbalanced by the toxin excretion. Receding morning temperatures necessarily follow.

SUMMARY.

Typhoid fever is essentially a septicemia. Mere blood invasion, however, does not produce evidence of disease. Intoxication occurs mainly through the destruction of the bacilli by the body cells and fluids. Intracellular poisons are thereby

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set free, and the individual then first shows signs of disease.

The intensity of the intoxication will depend upon the rate of destruction, modified, of course, by varying efficiency in elimination.

Rapid destruction of a few bacilli will cause a short, sharp attack of fever, ending perhaps by crisis.

Rapid destruction of a large number of bacilli will cause intense intoxication of longer duration. This produces the fulminating type of the disease and is frequently fatal.

Slow destruction of moderate numbers of bacilli will cause moderate intoxication of longer duration — the true " slow " fever.

If the gradually increasing immunity does not, within a reasonable time, check the growth of the bacilli, then the intoxication must gradually increase and the individual finally die.

As regards specific therapy in typhoid fever: In the absence of a true antitoxin we have had to fall back on the use of various bacterial products which have had for their aim the stimulation of the individual to destroy the invading bacilli with greater intensity.

Such treatment is suitable for those cases only which are not already hyper-intoxicated. In the presence of severe typhoid poisoning the indication may be to *check* in some way bacillary destruction. This might be accomplished (*a*) by inoculation of the nontoxic typhoid substances to divert destructive agents from the

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living toxin-bearing bacilli, or (*b*) by cold baths, to combat, by low temperature, rapid phagocytosis and bacteriolysis, or (*c*) by giving drugs which shall lower metabolic activity (quinine, etc.).

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PRIMARY SARCOMA OF THE PLEURA.

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(*From the Laboratory of the Department of the Theory and Practice of Physic, Harvard University.*)

THE following case is of interest on account of the great rarity of sarcoma primary in the pleura. The history of the case is unattainable other than that there was a tumor removed from the thyroid region at an earlier date, which proved to be a benign adenoma, and that for some time before this there were signs of fluid in the left chest with increasing dyspnea, for which the woman came to the hospital. The autopsy * showed the following:

Body of a large, well-developed, well-nourished woman. Diaphragm, right side to a height of fifth rib, on the left side to seventh rib. On the left side the diaphragm bulges down as compared with the normal dome shape.

Pleural cavities: Right pleural cavity is free from fluid. Pleura is smooth and glistening. Left pleural cavity is distended with a large amount of clear straw-colored fluid. This could not be measured but exceeded several liters. The entire pleural cavity on the left side is lined with a grayish layer, nowhere smooth, though its surface is very glistening. In general, the surface is coarsely granular and in places

* The autopsy was made by Dr. Henry A. Christian.

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thrown into coxcomblike folds, some several centimeters in length. This is more marked in that portion of the pleura lying in apposition with the pericardium. This tissue is firm and on section is seen to be on the average 3 mm. in thickness, and overlies a considerable layer of fat tissue. In this fat tissue adjacent to the mediastinum there are present a few lymph nodes grayish in color from 1 to 1½ ccm. in greatest diameter. Pleural cavity on the left side extends well to the median line and consequently part of the inner surface of the sternum is lined by this above-described tissue. The lung itself is greatly compressed and lies as a flattened mass along the spinal column. Pericardial cavity free from fluid and normal in appearance. Heart is of normal size, myocardium dark red in color; valves are normal. Coronary arteries show a moderate degree of thickening and in one there is a small calcified plaque.

Lungs: Right lung is voluminous; its surface is smooth; has the usual carbon marking. Scattered over its surface are a few small, firm, slightly projecting, rounded, grayish white areas. Section of these shows them to be small grayish white masses of solid, firm, though not hard, tissue. From the cut surface of the lung exudes a large amount of frothy fluid. Portions of the cut surface are gray, other portions grayish-red in color. There are a few scattered whitish nodules as described on the surface, none exceeding 5 mm. in diameter. The bronchi contain a small amount of muco-purulent material; the mucous membrane is slightly congested.

The left lung: The left lung is compressed into a flabby, wrinkled, solid mass. Its pleura is slightly thickened and presents an appearance similar to that described for the parietal pleura, though the process on the visceral pleura is not so marked. The lung is air-

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less. Its cut surface is gray or yellow-gray in color. Scattered through it, particularly along the lower posterior border, and extending from there up to the point of the entrance of the bronchi and larger vessels, there are irregular masses of firmer tissue, in general grayish or pinkish-gray in color, not sharply circumscribed from surrounding lung tissue. Elsewhere in the lungs there are a few small grayish nodules. Near the root of the lung there is an irregular cavity containing grayish-yellow puriform material, smears from which show cells of varying size and shape, some with mitotic figures. Some of these cells are well preserved, others necrotic. One lymph node in this region is of a cheesy consistence and a yellow color, like that of a hard-boiled egg. The bronchi on this side are similar to those on the right.

Abdomen: Stomach, intestines and pancreas normal. Spleen is slightly enlarged, purplish in color with smooth surface. Cut surface is dark red; Malpighian bodies are visible as grayish areas 1 to 2 mm. in diameter. From the cut surface a small amount of pulp can be easily scraped away.

Liver of normal size. Surface is smooth. Visible on the surface are a few small white or grayish areas, scarcely at all elevated above surrounding tissue. The largest of these lie in the superior surface of the left lobe and measure one cubic centimeter in diameter. The section of this latter shows a soft white tissue. Cut surface of the liver is of a uniform brownish gray color and of firm consistence. On close inspection numerous narrow grayish bands of connective tissues can be seen running along the lobules. This appearance is uniform and nowhere is there any marked connective tissue increase. On the cut surface a few small, grayish areas can be made out.

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Gall bladder normal.

Kidneys show no evidence of metastases.

Uterus normal except for a few fibromyomata.

Tubes and ovaries normal.

Organs of neck: High upon the right side beneath the ramus of the jaw there is a tumor mass about 5 ccm. in diameter, of firm consistence, which extends around to the internal carotid artery and reaches to the soft tissues posterior to the pharynx. In the region of the normal site of the thyroid no thyroid tissue could be found; the muscles apparently lie in close opposition to the trachea. Low down in the neck, just above the notch of the sternum, there is firm tissue similar to and continuous with that described in the pleura and which partially filled the anterior superior mediastinum, though there is no evidence of pressure on trachea or esophagus.

Larynx normal.

Esophagus normal.

Tongue normal. Trachea in lower half somewhat congested, otherwise normal.

ANATOMICAL DIAGNOSES.

Tumor of thyroid.

Extensive tumor growth in left pleura with hydrothorax and atelectasis of left lung.

Metastases in liver and lung.

Moderate cirrhosis of liver.

Fibromyomata of uterus.

MICROSCOPIC EXAMINATION.

Liver: There is a moderate diffuse increase of the connective tissue at the periphery of liver lobules. In

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some lobules a considerable amount of fat is present in the liver cells in the peripheral half of the lobule.

Spleen: In some of the Malpighian bodies are small rounded masses of a hyaline material. In the pulp are scattered cells containing coarse granules of bright yellow pigment. Stroma not increased.

Kidney appears normal.

Tumor of neck: Nodule from submaxillary region is an adenoma papillomatous in character in most parts. In the simple parts we have small rounded spaces lined by a single layer of low cuboidal epithelium and filled with colloid. In the papillomatous parts ingrowth has taken place into larger spaces, so that they are almost completely filled by masses composed of a narrow connective tissue stalk, covered by epithelium similar to that lining the gland spaces.

Here the property of forming colloid is retained to a certain extent. Throughout the epithelium is regular and shows no evidence of rapid growth. The stroma in all parts is non-cellular and slow growing.

Tumor of pleura is of sarcoma type, made up of irregularly-shaped cells of varying size, the majority presenting a spindle shape. (Figs. 1 and 2.) However, there are many cells, round, oval or irregular in contour, large and small, some with one nucleus, others with several nuclei. In places large cells like giant cells can be seen. (Fig. 2.) In several places the spindle cells are quite closely packed, but for the most part the structure is loose and has very little intercellular substance to form a connective tissue stroma. Mitoses are numerous. The tumor forms a distinct layer along the pleura and everywhere invades the subpleural adipose tissue, the tumor cells arranging themselves in whorls around the fat cells. (Fig. 1.) The tumor is quite vascular and many small blood vessels

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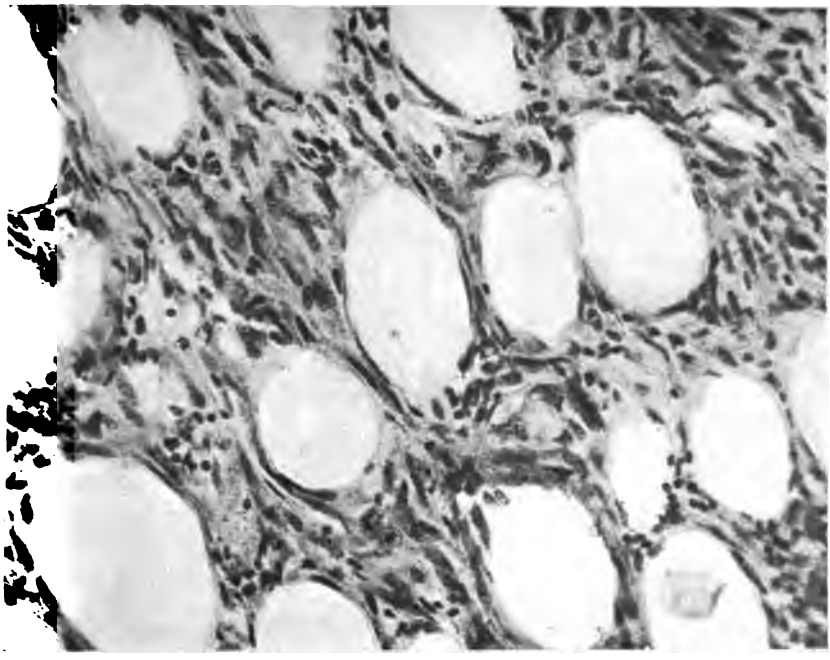
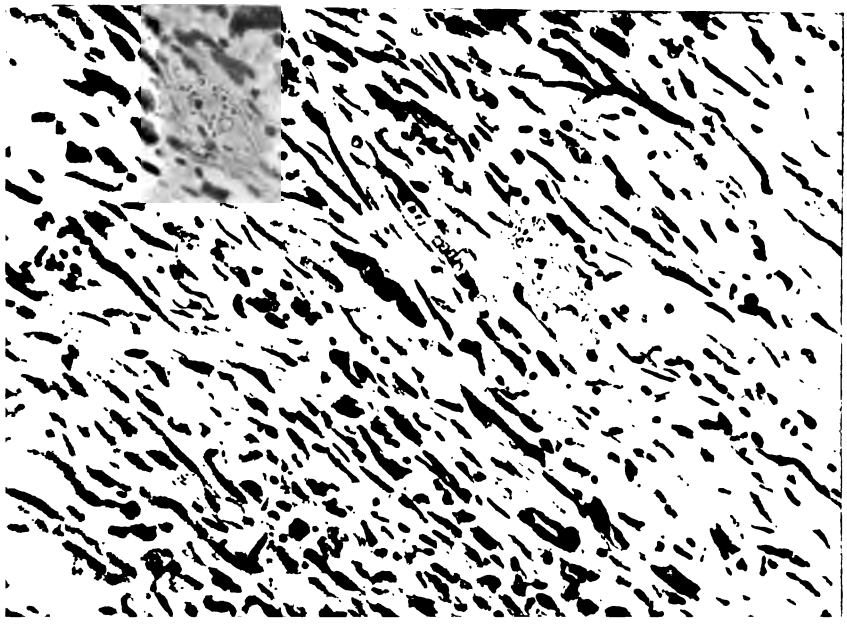


FIG. 1.



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a predominant feature of the growth contain fluid and coagulated blood. The softened puriform material on microscopic examination proved to consist of stellate and pyriform cells. Some sections show coarse fibrous net work enclosing red blood corpuscles in its meshes and many large thin-walled vessels filled with blood. In its more solid parts the growth is composed of closely packed round cells with very scanty stroma. Many of the individual cells contain clear rounded spaces or drops, apparently the result of mucoid degeneration. Many branching cells are seen with clear mucoid drops in them. No metastasis in any other organ.

CASE VII. Finlay [7] reports a case in a man sixty-seven years old. Autopsy showed bloody fluid in left chest. Left pleura easily stripped from chest wall. Both layers thickened, 5 mm. in thickness. Inner surface studded with nodules of white or reddish color, which on section are uniformly white and juicy. The nodules are from 5 mm. to 30 mm. in thickness, 8 to 60 mm. in diameter. Left lung is collapsed. One bronchial gland slightly enlarged, no metastasis in other organs. Microscopic examination shows the tumor to consist of large irregular-shaped, multinuclear cells with smaller round and oval cells between. Stroma not evident. Blood channels visible between rows of cells. Diagnosis, myeloid sarcoma.

CASE VIII. Kaufman [8] reports a case in a woman of twenty-nine years, where sarcoma, the size of a child's head, of soft consistency, was found in the right pleural cavity in the lower part. The diaphragm was involved in the growth. Microscopic examination showed a polymorphic cell sarcoma. The cell masses were arranged like mantels around wide thin-walled vessels. The vessels in many places were thrombosed and the

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a strong acid is added to the urine to neutralize it, such a violent reaction occurs with the liberation of CO_2 as to destroy the casts and interfere with filtration. The turbidity was most satisfactorily overcome by adding to the urine to be centrifugalized a small amount of very dilute acetic acid solution. This is not strong enough to cause the liberation of CO_2 and yet helps very much in the examination of the sediment. To get the urine clear for determining albumin, the same dilute acetic acid was used and the urine filtered several times if necessary. Care must be taken not to add too much acid, a drop or two in a half wineglass of urine is usually sufficient, for the urine becomes turbid again with an excess of acid.

Each animal was watched for a day or two when first put into the cage before it was given any injections, for it is well known that in confinement rabbits often show albuminuria and cylindruria. In every instance the rabbit was allowed to become albumin- and cast-free before starting the experiment. To prove that this was necessary a rabbit which had received no injections, but had albumin and casts in the urine, was killed, and the kidney on section showed marked cloudy swelling of the epithelium of many of the convoluted tubules in certain areas, but this process was not as general as in the earlier stages of the toxic nephritis, and no tubules showed actual necrosis.

In general, the examination of the urine for albumin did not reveal anything remarkable. In regard to the appearance of casts, however, it is to

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be noted that the fine, granular casts were the first to appear in every instance, with one or two exceptions. The hyaline casts came later. There was a greater variation in the size and shape of the casts than is commonly seen in human nephritic urine, and there was a tendency for the casts to appear in showers, only a few or even none might be seen on one day and great numbers the next. These cast-showers were usually accompanied by a corresponding rise in the quantity of albumin. As one would expect, the animals in which the main kidney lesions were glomerular did not show so many casts in the urine as those in which the tubules were primarily affected, but they did show a relatively large amount of albumin.

Whenever possible, the animal was killed, not allowed to die, and by this means post-mortem changes were eliminated and the better sections from fresh tissues were secured. In this study the description of the kidney sections was limited to those phases of the process associated with cast formation and many epithelial changes and cellular infiltrations neglected, as they had no bearing on this particular phase of the subject. It is hoped that a careful study of the sections may be reported at some other time. All tissues were hardened in Zenker's fluid and embedded in paraffin. The sections were stained with eosin and methylene blue.

URANIUM NITRATE.

The various stages of the process of cast formation were clearly shown in the kidney sections

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from animals which had received injections of this drug. The first change noted was a swelling of the cells composing the convoluted tubules, by which process the cell boundaries are lost and the lumen of the tubule obscured. (Fig. 1.) The straight tubules were also affected in a similar manner, but to a much less extent. From this swelling the cells went on to a marked degeneration in which the whole tubule often became destroyed and in its place there remained a granular necrotic mass, staining a dark pink with eosin and methylene blue. (Fig. 2.) Scattered through this mass the cell nuclei could be made out, often nearly normal in appearance, but in many instances altered so that their fine, reticular structure was entirely lost and the chromatin granules massed together in a single dark speck. The distal convoluted tubules appear to be affected by the degenerative changes earlier than are the proximal. This is shown in Fig. 8, in which an almost normal tubule is seen at its origin from a glomerulus, whereas tubules more distant show degenerations. Later, both groups of convoluted tubules show injury. At this stage of the process there were no casts to be seen in the collecting tubules, showing that their origin is not co-incident with the lesions in the convoluted tubules, but is dependent upon it. These stages are well illustrated in many of the animals and are seen exclusively in those given a single injection and killed at the end of twenty-four hours.

The following are illustrative protocols:

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Rabbit No. 5. First day. 1,040 gm., rabbit caged.

Second day. Urine showed no albumin, no casts. Given .005 gm. of uranium nitrate subcutaneously.

Third day. Urine showed albumin, very slight trace. No casts. Animal killed.

Kidney: macroscopically normal. Microscopically, glomeruli apparently normal. Cells lining the convoluted tubules necrotic, many times cell boundaries completely lost and lumen filled with a granular material. The nuclei are very prominent, some of them have lost their characteristic appearance and look simply like a dark mass, with eosin and methylene blue stain. No fine reticular structure can be made out. The collecting tubules do not show any variation from the normal, their lumen is free from granular material.

Rabbit No. 2: First day. 635 gm., rabbit caged.

Second day. Urine: no albumin, no casts.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .004 gm. uranium nitrate subcutaneously.

Fifth day. Urine: albumin, slight trace. Rare cast with cells adherent. Given .004 gm. uranium nitrate subcutaneously.

Sixth day. Urine: albumin, slight trace. Rare granular cast.

Seventh day. Urine: albumin, slight trace. Few granular casts. Animal found dead.

Kidney: Macroscopically, dark colored and the markings distinct. Microscopically, glomeruli apparently normal. Convoluted tubules everywhere necrotic, cell boundaries and lumen indistinct; in many places the whole tubule is a mass of granular material with nuclei scattered through it. Epithelium of collecting tubules normal. In some of the tubules at some distance from cortex the lumen contains the degen-

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erated cells, but less granular in appearance, and only rarely is a nucleus seen. These tubules take deeper stain with eosin and methylene blue stain.

Rabbit No. 9. First day. 930 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .002 gm. uranium nitrate.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .002 gm. uranium nitrate.

Sixth day. Urine: albumin, trace, occasional granular cast, some with cells adherent.

Seventh day. Urine: albumin, large trace, rare granular cast.

Eighth day. Urine: albumin, slight trace, no casts. Animal found dead.

Kidney: Macroscopically, appears slightly pale, seems boggy. On section tissue is injected, but markings are distinct. Microscopically, glomeruli appear normal. In cortex convoluted tubules are necrotic; in some places there is almost no evidence of the lumen, and when intact the lumen is often filled with granular detritus. The straight tubules are involved in the destructive process to a slight extent. The epithelium of the collecting tubules is mostly intact, but the lumen often contains a granular plug or cast.

A further stage in the process of cast formation was seen in tubules in which the epithelium was necrotic, but the cell boundaries remained for the most part distinct. The lumen of those tubules was preserved, but filled with a granular detritus similar in appearance to the material composing the necrotic cells lining the tubules. Apparently this was the result of the necrosis of

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the cells of the tubules, for it was not found in a single mass, but was broken up into segments or sections representing in outline degenerated epithelial cells, and most of these had a darkly staining mass within them, the remnant of a destroyed nucleus. (Fig. 3.)

The following animal illustrates this point well:

Rabbit No. 1. First day. 1,350 gm., rabbit caged.

Second day. Urine: no albumin, no casts.

Fourth day. Urine: no albumin, no casts. Given .005 gm. uranium nitrate.

Fifth day. Urine: albumin, trace. Few casts, some of them only very slightly granular, with cells adherent. Very rarely an epithelial cast. Given .005 gm. uranium nitrate.

Sixth day. Urine: albumin, large trace. Considerably many granular casts, rarely with cell adherent. Given .005 gm. uranium nitrate.

Seventh day. Urine: albumin, large trace. Numerous granular casts, some with cells adherent.

Kidney: Macroscopically, firm and pale. Markings not very distinct. Microscopically, glomeruli appear normal. Epithelium of the convoluted tubules necrotic, cell boundaries and lumen often obscured. Certain tubules, especially those removed from the cortex, are better preserved and their lumen filled with granular material. This is often separated into irregular divisions, appearing like the remnants of cell divisions, and partially degenerated nuclei may be seen within the segments. Some tubules, themselves normal, contain a nearly homogeneous mass, separated from the lining epithelium by a clear space, evidently a hyaline cast. Collecting tubules are normal, but contain a good many casts.

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The next stage in the process of cast formation was seen in sections which show in the tubules farther removed from the cortex a much less marked necrosis of the epithelium, but the lumen contains granular material. This had lost its sectional or broken-up appearance and the necrotic remains of the individual cells had become much more closely massed together, though in many instances the cell boundaries could be distinguished. (Fig. 4.) Next, the cast appeared as a very finely granular mass in which no remnant of the cell origin was evident (Fig. 5), and finally the granular characteristic of the casts was less prominent and the hyaline nature appeared. (Fig. 7.) It is interesting to note that the more granular the cast the less well preserved was the epithelium of the tubule in which it was found. The necrotic material coming from the convoluted tubule is apparently forced along by the urinary stream and molded into shape by the tube through which it passes. At first the detritus is very loosely formed and coarsely granular, but as it passes down the tubule it comes together into a compact mass and becomes more finely granular and eventually hyaline. It is possible also that some change is taking place at the same time in the material which composes the cast and that this results in a fusion of the original granular substance into a homogeneous mass. Certain sections showed cells attached to the granular plug within the lumen of the tubule. (Fig. 6.) These appear to have been deposited on

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the partially formed cast as it moved downward in the urinary stream.

This stage is shown in the following animals:

Rabbit No. 3. First day. 825 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .004 gm. uranium nitrate.

Third day. Urine: albumin, very slight trace. Very many granular casts, occasionally with cells adherent. Given .004 gm. uranium nitrate.

Fourth day. Urine: albumin, trace. Many casts, many with cells adherent. Given .004 gm. uranium nitrate.

Fifth day. Urine: albumin, trace. Few granular casts. Animal killed.

Kidney: Microscopically, pale, rather firm and edematous, markings moderately distinct. Microscopically, glomeruli apparently normal. Convoluted tubules near the cortex very necrotic, the lumen destroyed, and tubule replaced by a finely granular mass with nuclei fairly well preserved. Farther from the cortex the epithelium of the tubules is somewhat less necrotic, but for the most part granular, and the lumen contains a granular plug. The collecting tubules show a normal epithelium, but casts within the lumen separated from the lining cells by a free space. The casts in some instances appear like swollen, degenerated cells, the boundaries between which can be faintly made out and the remnants of nuclei seen.

Rabbit No. 7. First day. 1,020 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .005 gm. uranium nitrate.

Third day. Urine: albumin, slight trace. Considerably many granular casts, occasionally with cell adherent.

Fourth day. Urine: albumin, large trace, many granular casts.

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Sixth day. Urine: albumin, large trace, many granular casts.

Seventh day. Urine: albumin, slight trace, no casts. Animal killed.

Kidney: Macroscopically, slightly pale. Markings distinct. Microscopically, glomeruli appear normal. Cells of convoluted tubules are necrotic, but lumen is fairly well preserved; many casts in collecting tubules, many of them showing cells adherent. A considerable number of casts are denser and darker staining. Many mitotic figures are seen throughout the section.

The epithelium of the collecting tubules was in most instances normal, but the lumen contained casts carried along by the urinary stream. These casts appeared much more uniformly granular and were entirely distinct from the lining of the tubules, being separated from it in most instances by a clear space. Occasionally the cast had lost its granular appearance and become homogeneous, taking a darker stain with eosin and methylene blue; in other words, it was a hyaline cast.

The following animal showed this:

Rabbit No. 11. First day. 985 gm., rabbit caged.

Second day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

Third day. Urine: no albumin, no casts.

Fourth day. Urine: albumin, slight trace, many fine granular casts.

Fifth day. Urine: albumin, slight trace, many fine granular casts:

Sixth day. Urine: albumin, trace, few granular casts, some with cells adherent. Animal dead.

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Kidney: Macroscopically, rather dark, markings distinct. Microscopically, glomeruli apparently normal. Convoluted tubules show necrosis of the epithelium as in previous sections, but in much less marked degree. Collecting tubules contain only a very few casts, but these are separated from the lining epithelium by a clear space and are not connected with those cells in any way. The casts are for the most part granular, but occasionally hyaline.

The kidney sections from an animal [3] allowed to run for a long time showed very different lesions, simulating closely those of chronic interstitial nephritis. There was considerable increase in the connective tissue, much dilatation of the tubules and glomerular spaces and some apparent increase in the cellular elements of the glomerular tufts. (Figs. 9 and 10.) The convoluted tubules which were not dilated showed some necrosis. In these the lumen was mostly obscured and the tubule filled with the granular material as described in connection with the more acute processes. Only a very few of the collecting tubules showed any casts, and those present were much more homogeneous in appearance, a few were hyaline.

This animal showed the following:

Rabbit No. 10. First day. 800 gm., rabbit caged.
Second day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

[3] In this case a spontaneous chronic lesion cannot be absolutely excluded. Confirmation of other experiments is needed to prove the assumed relation between the uranium and the lesions.

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Fourth day. Urine: no albumin, no casts. Given .001 gm. uranium nitrate.

Sixth day. Urine: albumin, trace. Rare fine granular cast. Given .001 gm. uranium nitrate.

Seventh day. Urine: albumin, trace. Rare fine and coarse granular cast.

Eighth day. Urine: albumin, trace. Very rare cast.

Ninth day. Urine: albumin, large trace. Very rare granular cast.

Tenth day. Urine: albumin, trace. Occasional granular cast.

Eleventh day. Urine: albumin, very slight trace. Occasional granular cast.

Thirteenth day. Urine: albumin, very slight trace. Occasional granular cast.

Fifteenth day. Urine: albumin, slight trace. Rare hyaline cast.

Seventeenth day. Urine: albumin, slight trace. Rare hyaline and fine granular cast.

Nineteenth day. Urine: albumin, slight trace. Very rare granular cast.

Twentieth day. Urine: albumin, slight trace. Occasional granular cast.

Twenty-first day. Urine: albumin, slight trace. Rare fine granular cast.

Twenty-third day. Urine: albumin, slight trace. No casts.

Twenty-sixth day. Animal killed.

Kidney: Macroscropically, small, pale, slightly granular and markings not very distinct. Microscopically, considerable increase in the connective tissue and in the cellular elements in the glomerular tufts. The tubules are much dilated and there is an increase of the space within the capsule of the glomeruli. The epithe-

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lium of the convoluted tubules which are undilated show a fair amount of necrosis, with obscuring of the lumen and filling of the tubule with granular material as seen before. Only a few of the tubules show any casts, but they are more homogeneous than in other sections and a few are hyaline.

POTASSIUM BICHROMATE.

Potassium bichromate produces lesions which in the main are like those of uranium nitrate; that is, the convoluted and straight tubules are attacked and the glomeruli remain normal. In most cases with potassium bichromate there was a more general destruction of the tubular epithelium, and in some instances the collecting tubules were also involved in the necrosis. The process of cast formation could be seen here also. The granular detritus coming from the broken-down epithelial cells of the convoluted tubules was massed together and had taken on the form and shape of the tubule through which it passed. In the early stages of the process, and high up in the secretory system, the casts were always granular, but later and farther along they became either more homogeneous or truly hyaline.

These animals are typical of a number of experiments with injections of potassium bichromate.

Rabbit No. 30. First day. Rabbit caged.

Second day. Urine: no albumin, no casts. Given 1 ccm. of 5% solution of potassium bichromate.

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Third day. Urine: albumin, slight trace. No casts. Animal killed.

Kidney: Macroscopically, normal in appearance. Microscopically, glomeruli appear normal. Marked necrosis of the convoluted tubules and to slight extent of straight tubules. Often there is complete destruction of the tubules and the place taken by a granular mass with nuclei in the midst. No casts seen in collecting tubules.

Rabbit No. 12. First day. Rabbit caged.

Second day. Urine: albumin, slightest possible trace. No casts.

Third day. Urine: albumin, slightest possible trace. No casts.

Fourth day. Urine: albumin, slightest possible trace. No casts. Given ½ ccm. 5% solution of potassium bichromate.

Fifth day. Urine: albumin, very slight trace. Very rare granular cast.

Sixth day. Urine: albumin, very slight trace. Occasional granular cast.

Seventh day. Urine: albumin, very slight trace. Occasional fine and coarse granular cast.

Eighth day. No urine. Animal found dead.

Kidney: Microscopically, glomeruli apparently normal. Very widespread destruction of tubular epithelium, only few areas where there is normal epithelium The convoluted tubules are necrotic and lumen obscured, their place being taken by granular material. The straight tubules are less affected, though some of them are granular in appearance and the lumen is usually filled with casts in the process of formation. The collecting tubules contain many granular casts and a rare hyaline cast; these latter are always in tubules whose epithelium is normal.

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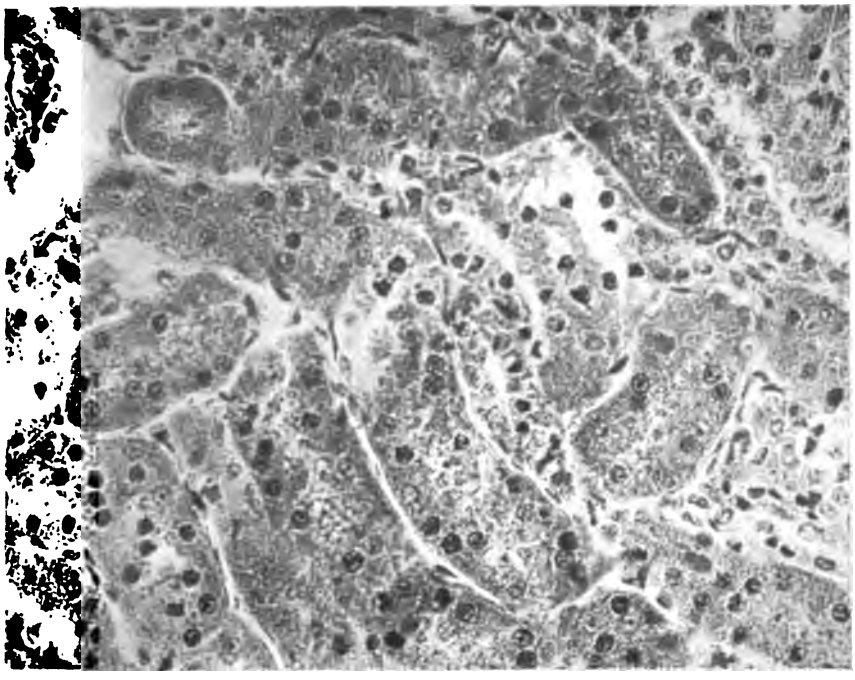

FIG. 1.

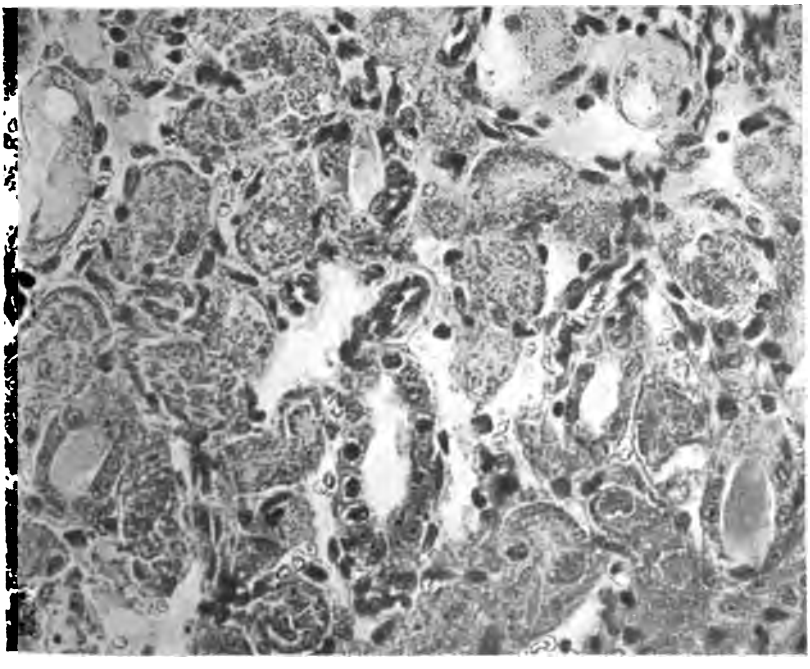

FIG. 2.

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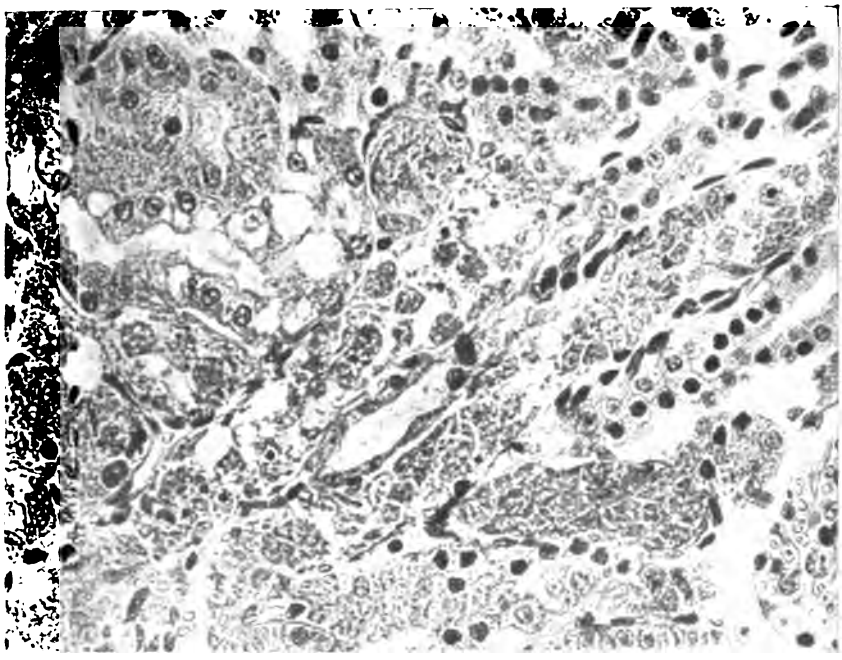

Fig. 3.

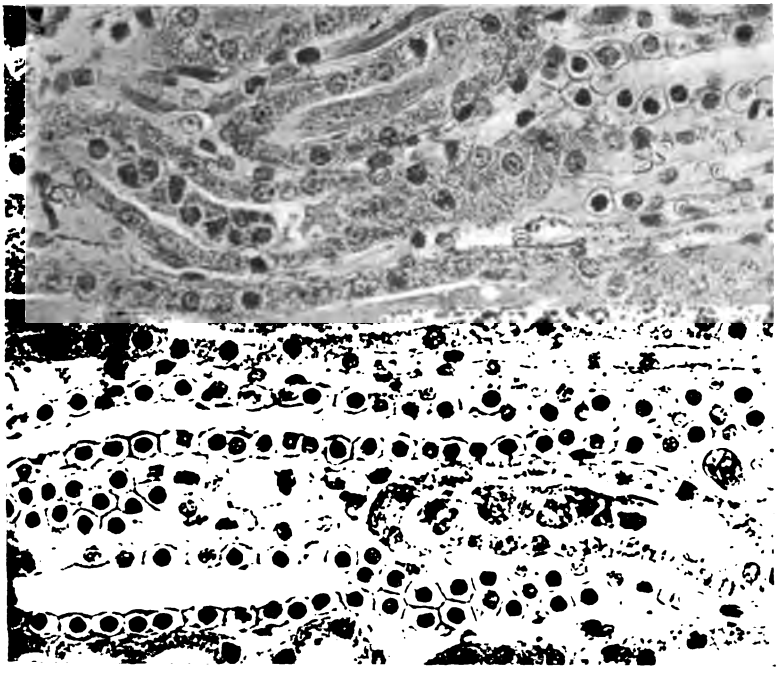

Fig. 4.

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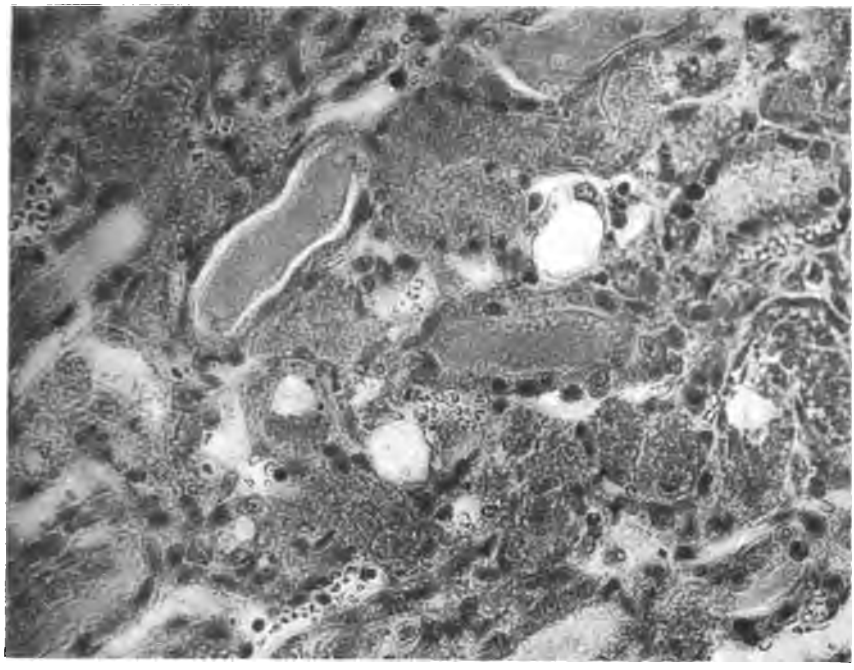

FIG. 5.

FIG. 6.

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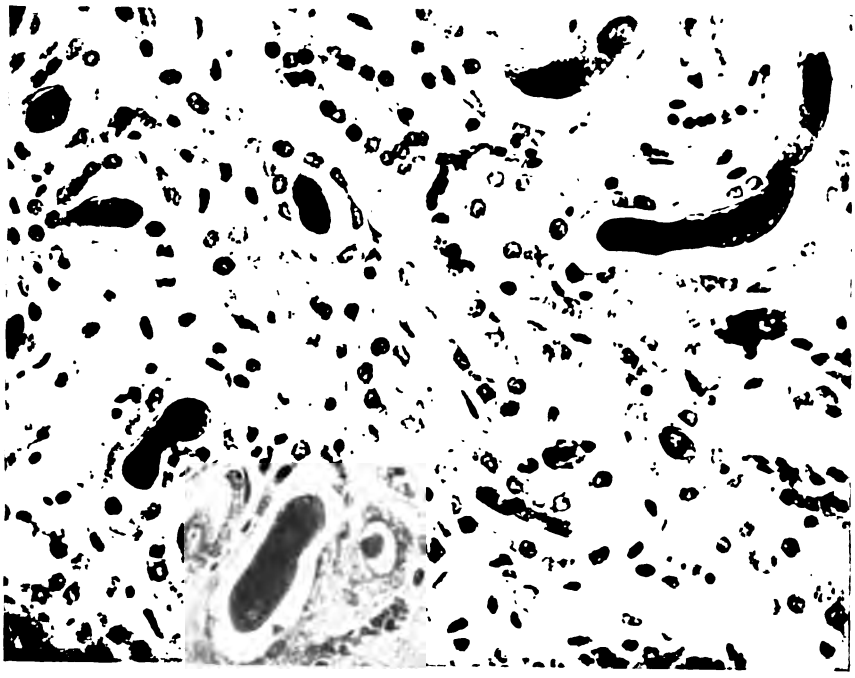

FIG. 7.

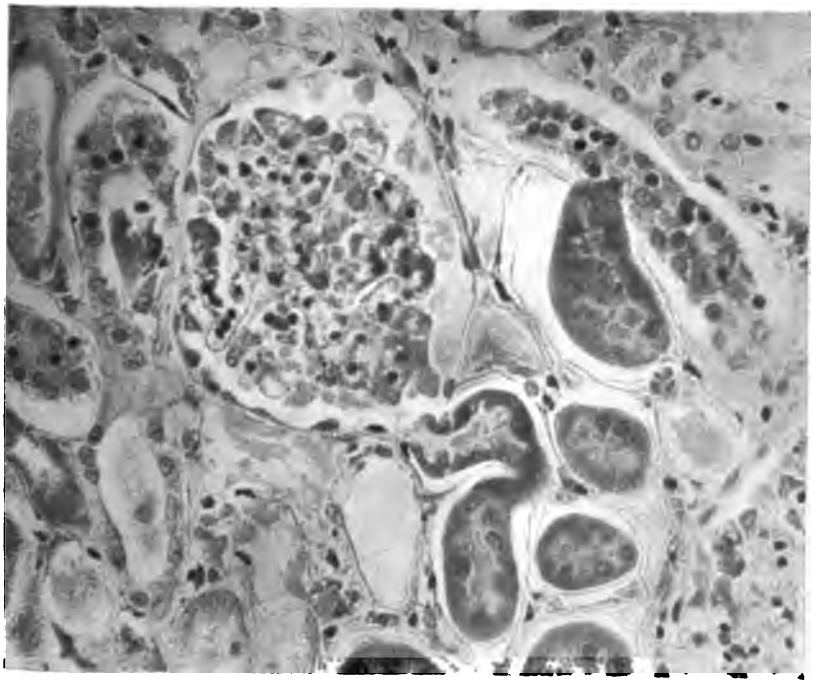

FIG. 8.

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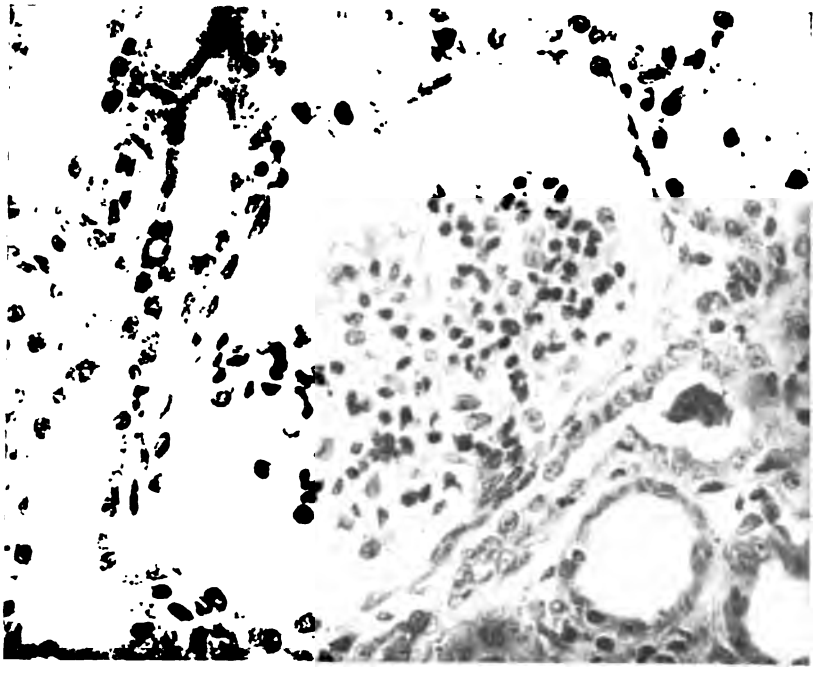

Fig. 9.

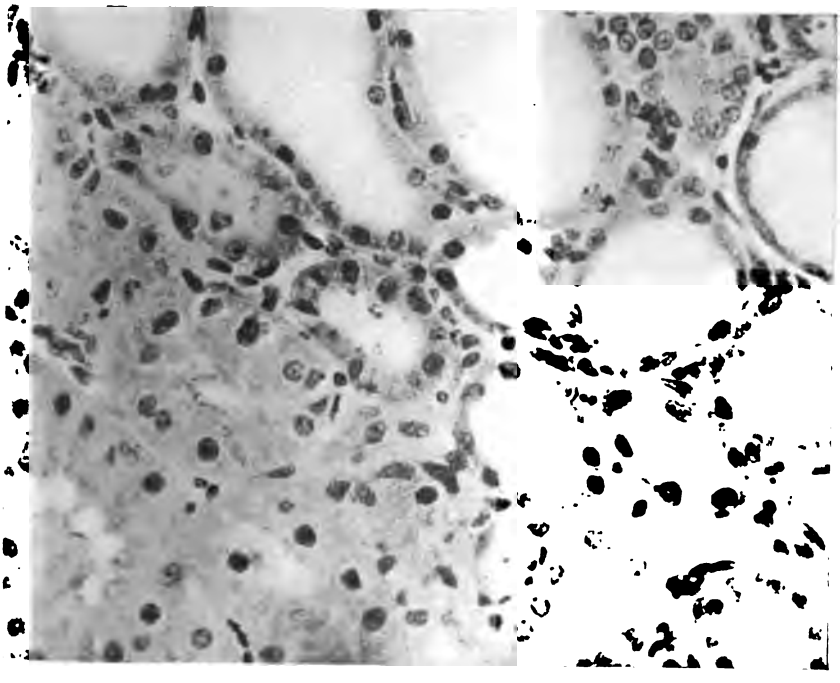

Fig. 10.

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Rabbit No. 15. First day. Rabbit caged.

Second day. Urine: no albumin, no casts. Given 5 ccm. of 5% solution of potassium bichromate.

Third day. Urine: albumin, very slight trace. Rare granular cast.

Fourth day. Urine: albumin, very slight trace. Rare granular cast. Given .5 ccm. of 5% solution of potassium bichromate.

Fifth day. Urine: albumin, very slight trace. Rare granular cast.

Sixth day. Urine: albumin, large trace. Very many fine granular casts of various sizes. Few hyaline casts, mostly of large caliber.

Eighth day. Urine: albumin, trace. Many casts, fine and coarse granular, few with cells adherent. Few hyaline casts.

Ninth day. Urine: albumin, slight trace. Many casts, fine and coarse granular, and hyaline. Some cells and fat on casts.

Tenth day. Urine: albumin, large trace. Many casts, hyaline predominating. Animal found dead.

Kidney: Macroscopically, apparently normal. Microscopically, glomeruli apparently normal, though they seem rather cellular. There is necrosis of the cells of the convoluted tubules, especially those close to the capsule. In most cases the lumen is preserved, but filled with granular material. There are many casts, most of them granular, some hyaline.

TRYPAN RED.

The urinalysis of animals which are given injections of trypan red did not show many casts, but the casts had a tendency to appear in showers, great numbers one day and very few the next. A few hyaline casts were seen. The albumin was

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not present in large amounts and the animals did not seem sick, so that it was inferred that the experiments might not prove very satisfactory. Study of the kidneys confirmed this to a certain extent. All the tissue appeared very red and the markings were not distinct. On microscopic examination of the kidney sections the most striking thing was the great increase in cellular elements, especially in the glomeruli in the early stages and in the connective tissue in the cases of longer standing. The blood vessels contained a great many red blood corpuscles. There was very little necrosis of any of the tubular epithelium, but in a few places the casts in process of formation could be seen. Some of the cells showed the initial swelling with the loss of cell boundaries and destruction of lumen, and in other places real necrosis was present. Then further along the granular material was seen within the tubule, and finally a well-formed cast.

This experiment may be given as typical of those performed with this substance.

Rabbit No. 19. First day. Animal caged. Given 20 minims trypan red.

Second day. Urine: no albumin, no casts.

Third day. Urine: albumin, slightest possible trace. Rare granular cast.

Fourth day. Urine: albumin, slightest possible trace. Rare granular cast. Given 20 minims trypan red.

Fifth day. Urine: albumin very slight trace. Occasional granular cast.

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Tenth day. Urine: albumin, slight trace. Occasional granular cast. Given 20 minims trypan red.

Twelfth day. Urine: albumin, trace. Many granular and occasional hyaline casts.

Fifteenth day. Urine: albumin, very slight trace. Occasional hyaline and fine granular casts.

Seventeenth day. Urine: albumin, very slight trace. Few hyaline and fine granular casts. Given 20 minims trypan red.

Twentieth day. Urine: albumin, very slight trace. Occasional granular and rare hyaline cast.

Thirty-second day. Urine: albumin, very slight trace, no casts. Given 80 minims trypan red.

Thirty-fourth day. Urine: albumin, very slight trace. Rare granular cast.

Thirty-sixth day. Urine: albumin, slightest possible trace. Many fine granular casts.

Thirty-eighth day. Urine: albumin, very slight trace. Occasional granular casts.

Fortieth day. Urine: albumin, very slight trace. Many granular casts. Animal killed.

Kidney: Macroscopically, very dark red, markings not distinct. Microscopically, section is very cellular, especially the connective tissue. The glomeruli contain in addition to the increase in the cellular elements many red blood corpuscles. The tubules are very well preserved, but a few scattered necrotic tubules may be seen. They are almost entirely the convoluted tubules, rarely the straight tubules. Only a very few casts can be found.

ARSENIC.

The experiments with Fowler's solution were also unsatisfactory. Very few casts were found in the urine and the kidney sections revealed little

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of interest relative to cast formation. The glomeruli appeared very cellular, but there was only slight necrosis of the tubular epithelium. There was a good deal of blood pigment seen in the sections. This case will illustrate the experiments with arsenic.

Rabbit No. 18. First day. Rabbit caged.

Second day. Urine: no albumin, no casts.

Third day. Urine: no albumin, no casts. Given 1 minim Fowler's solution.

Fourth day. Urine: albumin, slightest possible trace. Rare granular cast. Given 2 minims Fowler's solution.

Fifth day. Urine: albumin, slightest possible trace. No casts.

Sixth day. Urine: albumin, slightest possible trace. Occasional fine granular cast.

Seventh day. Urine: albumin, slightest possible trace. Very rare granular cast. Given 2 minims Fowler's solution.

Eighth day. Urine: albumin, slight trace. No casts. Animal found dead.

Kidney: Microscopically, glomeruli very cellular, filling whole space. Very little necrosis of convoluted tubules and only a small amount of granular detritus. Rarely can any casts be seen. There is a considerable amount of blood pigment free in the tubules.

CANTHARIDIN.

Cantharidin produces lesions in the glomeruli and tubules, but not of the same character as the other irritants. There was very little necrosis of the tubular epithelium and consequently little chance to study cast formation. Many single cells are seen free in the tubules evidently broken

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away from the lining epithelium. The whole section is cellular, especially the glomeruli, and the blood vessels are everywhere very distinct. One experiment is cited.

Rabbit No. 29. First day. 600 gm., rabbit caged.

Second day. Urine: albumin, slightest possible trace. No casts. Given .001 gm. cantharidin.

Third day. Urine: albumin, slightest possible trace. No casts.

Fourth day. Urine: albumin, very slight trace. No casts. Given .001 gm. cantharidin.

Fifth day. Urine: albumin, trace. Considerably many casts, fine granular, sometimes with cells adherent, occasionally blood adherent.

Sixth day. Urine: albumin, large trace. Many casts, fine granular and hyaline with cells and blood adherent. Some highly refracting.

Seventh day. Urine: albumin, large trace. Only very rare granular cast. Animal killed.

Kidney: Microscopically, section appears very cellular, and many red blood corpuscles may be seen. The lesion of the convoluted tubules is apparently a desquamative one, for large numbers of cells are free in the tubule, but there is very little necrosis of the cells composing the tubule. Very few casts may be seen.

These experiments with trypan red, arsenic and cantharidin are valuable in this connection, not because they furnish material for study of cast formation, but because they furnish negative evidence in support of the described histogenesis of the process. These animals had albuminuria, but very few casts in the urine, and the kidney sections showed

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few casts in the tubules. The lesions only to a very slight extent involved the tubular epithelium, but were largely in the glomeruli and connective tissue. As far as it goes this is in support of the theory that it is from the necrosis and destruction of the tubules and not from albumin excreted through the glomeruli that casts arise. This theory of cast formation is positively supported by the histological evidence adduced in connection with the degenerative lesions of the tubular epithelium and by the results of urine analysis.[4]

CONCLUSIONS.

From these experiments it would seem that the following conclusions may be drawn:

1. It is possible by the injections of uranium nitrate and other irritants to produce in rabbits an albuminuria and cylindruria dependent upon lesions of the kidney simulating nephritis in man.

2. Granular casts are the first to appear in the urine when the kidney is attacked by an irritant.

3. Casts are more common in the urine when the kidney lesion is primarily a necrosis of the tubular epithelium.

4. Casts arise from the degeneration and necrosis of the cells of the tubular epithelium of the kidney. Entire necrotic cells may desquamate and at first remain distinct from one another, then become massed together, and finally formed into a definite plug, taking the shape of the tu-

[4] I wish to express my thanks to Dr. Christian for his constant interest in the experiments, and also for his kind assistance in the preparation of this report.

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bule in which it is formed. The sam
takes place with cell fragments and
material derived from disintegrated c
casts are all granular at first and late
hyaline as they pass down the tubu
urinary stream.

DESCRIPTIONS OF PLATES.

FIG. 1. Shows swelling of cells of convoluted tubule
of cell boundaries and obscuring of lumen.
FIG. 2. Shows necrosis of cells of convoluted tub
necrotic mass breaking away.
FIG. 3. Shows necrotic material within tubules, b
tional in appearance; few nuclei evident in the mass.
FIG. 4. Casts within tubules, appearing as solid plu
ing origin from cells.
FIG. 5. Granular casts within tubules.
FIG. 6. Granular cast within tubule, cell adherent to
FIG. 7. Hyaline casts within normal tubules.
FIG. 8. Apparently normal gomerulus and a norma
ing from it.
FIG. 9. Shows a glomerular tuft in a dilated glomeru
FIG. 10. Shows dilated tubules in a chronic case.

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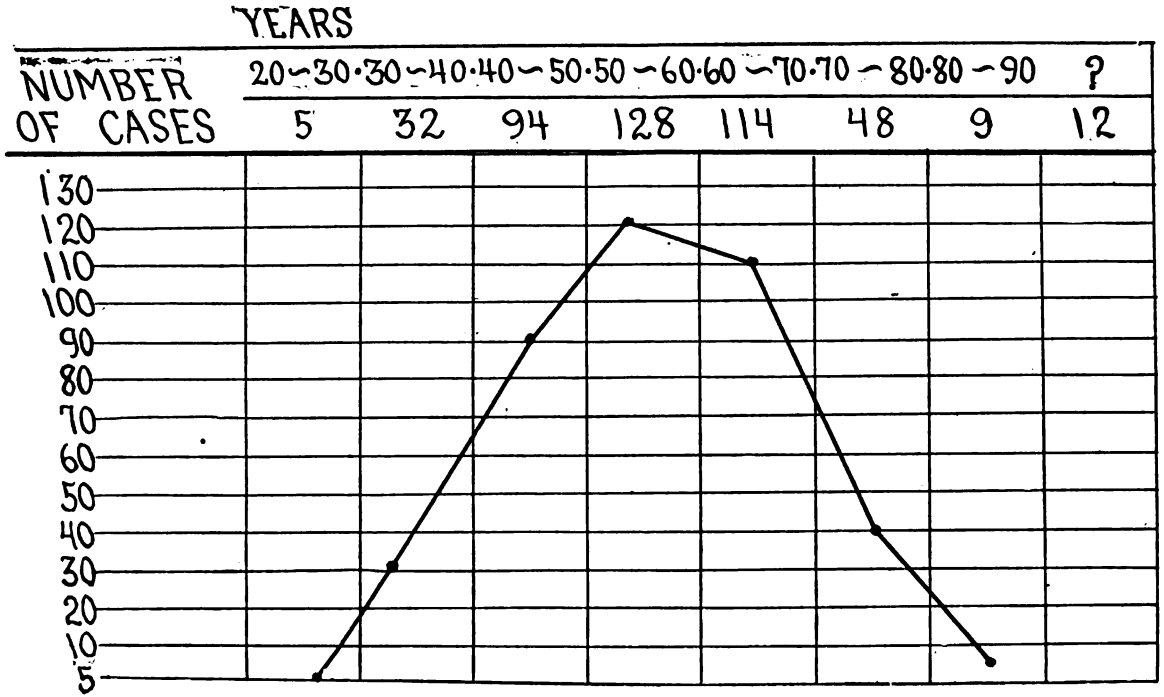
CHART 1.



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TUBERCULOUS PERITONITIS.

A STUDY OF 122 CASES TREATED AT THE MASSACHUSETTS GENERAL HOSPITAL BETWEEN 1900 AND 1907.

BY ARTHUR K. STONE, M.D., BOSTON,
Assistant in Theory and Practice of Physic, Harvard University; Physician to Out-Patients, Massachusetts General Hospital; Physician to House of the Good Samaritan.

TUBERCULOUS peritonitis is a subject about which cluster many unsolved problems, although much has been written since König's second paper in 1892. The swing of the pendulum of opinion has been extreme. First there was the general feeling of hopelessness in regard to the outcome of cases diagnosed as tuberculous peritonitis, and then followed a period of extreme hope for all such as were seen in time to have a surgical operation. Many cases were found to recover. But as more and more operations were done, and men with large clinics were able to follow their results, it was found that all cases were not cured, so that by 1901 Borchgrevink, a Swedish surgeon, took extreme ground against operation, saying that operations were not curative but were harmful and delayed healing. Other foreign writers, surgeons for the most part, have since 1900 taken a decidedly conservative ground. Animal experiments have been introduced to show that early operations were of more than doubtful value. In the

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United States, Murphy and Mayo and Douglas have urged " aggressive surgery " on the ground that it materially influences the prognosis favorably.

Not only is there division among the writers in regard to operations as a therapeutic procedure but also there are wide differences of opinion as to how the infection is introduced to the peritoneum; whether it comes from the blood, from the passage of the bacilli through the intestinal wall, or from the Fallopian tubes to the peritoneum. The Gynecological Congress at Rome, in 1902, discussed but did not settle these questions.

The operators who believe that surgical interference is an actively remedial therapeutic measure are hopelessly divided as to the reason why a simple incision through the abdominal wall should bring about the destruction of the bacilli of tuberculosis in the tubercles covering the peritoneum. Neither is there any universality in the technic employed by the surgeons to accomplish their results. For the most part such methods, as attempting to disinfect the peritoneal cavity with antiseptics, have been given up as well as that of having the operation take place in the direct sunlight. Most operators advise against trying to separate adhesions of any density. Mayo, however, advocates careful search for the primary focus, in spite of adhesions.

The exudate in cases of tuberculous peritonitis has been considered as a harmful substance which should be removed. Bacilli have sometimes

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been found in the fluid, and it has been taken for granted that by means of the fluid the organisms were still more widely disseminated throughout the abdominal cavity. Others have held that the fluid contained toxins, and others have removed it for the discomfort produced, and Mayo would remove it that the ends of the Fallopian tubes might seal up so that the bacilli should not escape into the abdominal cavity from these organs. Gelpke and others advance the theory that the exudate rather contains bactericidal bodies and is an effort of nature to effect a cure and therefore should not be removed or, at least, until such time should have elapsed that would make it probable that the fluid was no longer potent when it should be removed with the hope that a new and more powerful exudate would re-form and the process of cure thus be accelerated.

The question of frequency in sex is in dispute, although it had been supposed that it was settled that women were more prone to be attacked than men.

From this very brief survey of the subject it will be seen that much more will have to be written before the questions of tuberculous peritonitis will be settled.

My personal interest in this subject was aroused by the opportunity which I had, during 1907, to follow for a long period of time several cases of tuberculous peritonitis that had not been operated upon. In these cases I saw patients with

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well-marked ascites, after some time, suddenly begin to improve, the fluid to disappear, the patient to take on flesh and strength and to appear perfectly well. In one of these cases there was an opportunity, after the lapse of several months, to inspect the peritoneum, which was opened for an intercurrent disease. At this time it was found that the intestine and omentum were still thickly coated with miliary tubercles. In another case fluid distending the belly quickly disappeared, and the patient (against my advice) was playing golf within four weeks, after a change of residence. This case has since had no return of the ascites.

From these patients it was evident that rapid improvement could take place in the exudative form of tuberculous peritonitis which, had an operation been performed, would have been attributed to the effects of the operation. This led me to a partial review of the literature; and it was clear that since 1900 there was much greater conservatism than formerly among the foreign surgical writers as to the curative value of simple operations. Even the Mayo brothers, though asserting that simple incision and drainage aids recovery in a remarkable way, were evidently dissatisfied with their results and began to substitute mutilating operations in order to obtain still better results. First they did total removal of the uterus, tubes and ovaries, but in their 1905 paper advocate only the removal of the Fallopian tubes. Therefore, we must con-

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clude that they, to a degree, are in harmony with the conservative foreign writers.

It must be admitted at the outset by any one who wishes to advocate a conservative line of treatment in tuberculous peritonitis that he must show good and sufficient reason for so doing, as the statistics up to date have, for the most part, shown much better results for the cases treated surgically than for those which have been treated without surgical intervention.

If one stops for a moment to think, there are many reasons why this should have been so in the past. The medical world owes much to König, in that he first brought forcibly to the attention of the profession the fact that tuberculous peritonitis was a common and also curable condition.[1] Previous to that, the hospital physicians, who have been the teachers, had with few exceptions seen only the last stages of tuberculous peritonitis in their wards. They knew it only as a hopeless condition. Most of the milder cases passed unrecognized by the practitioners, and either got well spontaneously or gradually passed into a hopeless condition, when they sought refuge for their last days under the sheltering roof of some hospital or almshouse. Even of late years the list of so-called medical cases includes a number of rejected surgical cases, — cases where even enthusiastic operators

[1] It is interesting to know that one of the first, if not the first, operation done in this country was performed by Dr. Z. B. Adams, of Framingham, in 1884, the same year as that in which König's first paper appeared. The patient is still alive and well.

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breaking down and discharging foul pus. Purulent peritonitis had been found at the operation. The patient had been attacked suddenly seven weeks before entrance to the hospital.

2. There was a general increase of pain and tenderness and an outbreak of purpura. Purulent peritonitis was found at the operation. The symptoms had existed for about one month.

3. The wounds broke down and patient became generally septic. The abdominal cavity could not be entered so dense were the adhesions. Symptoms had developed within six weeks.

4. Abscess resulting in a fecal fistula developed after the operation. Much clear fluid had been found and many adhesions. Several cheesy nodules were removed from the large intestine; there was also a general distribution of tubercles. The symptoms had appeared suddenly only twelve days before.

The previous histories of these cases made the findings unexpected, though when found the result was obvious.

Subsequent history. — So far as the after histories of the patients have been followed it has been found that of the 112 who left the hospital alive 27 have since died.[2]

Of these 12 were treated without operation, 15 with operation.

The duration of life in the 15 surgical cases was as follows:

[2] Since the above was written two medical patients were reported to have died soon after leaving the hospital.

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1 month or less,	3
1–2 months,	2
3 months,	3
7–8 months,	1
8–10 months,	2
1–2 years,	2

One lived five or six years, had married, and died of some sudden cerebral condition. One lived five years and died of phthisis at the end of that time.

The duration of life in the medical cases was as follows:

1 month or less,	2	both *in extremis*, when taken from the hospital,
1–2 months,	3	two apparently favorable (both refused operation, and one of phthisis.
4 months,	2	
5–6 months,	3	one of whom was operated upon one month later in Colorado: one died of phthisis.
8 months,	1	
2 years+,	1	died of "cough."

It has been possible to find out about the present (February, 1908) condition of 28 living patients, 25%, or one quarter of those leaving the hospital alive. There are undoubtedly others as 28 letters remain unanswered while 19 letters have been returned as undelivered.

Of the 28 who have reported as being alive, surgical cases numbered 17, medical cases numbered 11.[3]

Of the 11 medical cases 6 have been out between one and two years (many of these nearly

[3] Since the above was written 1 medical case has reported herself alive and well, 7 years after discharge.

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two years), one between three and four, 1 over five years, 2 over six years; 1 over seven years.

With two exceptions all report themselves in good health. One of these has had a pleuritic exudate in the left chest which has since disappeared. The other is reported as a slim, pale child, though complaining of nothing. One patient who was tapped and had masses in the abdomen after a period of nearly two years writes: " A more healthy, robust girl never lived than I am at the present time."

Of the 17 surgical cases, those reporting themselves, have been out of the hospital as follows:

Under 1 year,	2
1–2 years,	2
More than 2 years,	4
" " 3 "	3
" " 4 "	3
" " 6 "	3

One patient has returned to Ireland and though well has not worked since the operation, over three years ago.

One has a cough and is out each day; the wound still discharges (nearly three years).

One reports in fair condition but has loss of weight and night sweats if she overworks.

One (of a year's standing) is stronger and gaining; the wound still discharges.

One of only a few months' standing feels well, but belly is tender.

In addition to these there are ten others who have been heard from since leaving the hospital, but have not replied to recent letters.

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One heard from four months after leaving the hospital. Perfectly well. Little discharge from the scar.

Seven patients were heard from one year after leaving the hospital. One patient had gained 20 lb. No abdominal pain. Had a cough and expectoration.

One reported poor health with pains in lungs and back.

One had been very sick for twelve weeks in another hospital, but was in good condition.

One reported wound broken down and discharging.

One had gained 18 lb., felt well and was in Ireland.

One reported her general condition excellent Six months later she was operated for cystitis; no bacilli of tuberculosis found in the urine.

One has had no trouble since operation.

One, four years after the operation, came for distress in stomach to the out-patient department. Nothing was found on examination. Patient was in good physical condition.

One patient came to the out-patient department for headaches and vertigo, four years after the operation.

The last two cases belong in the *cured* class.

Of the seven cases reporting at the end of a year two were evidently in poor condition and one other had a cough and expectoration, nevertheless in good condition.

To recapitulate: Of the 122 cases treated there were in February, 1908:

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Dead,	39
Alive, 1908,	29
Heard from, but not in 1908,	10
Letters returned,	19
Not answered,	25
Total,	122

Of the 44 of whom there has been no report whatsoever, the conditions at discharge make it very probable that in a number there has been a fatal ending.

It is specially unfortunate that 25 letters should remain unanswered, as this large number would have made the statistics so much more valuable.

The family history.— In 10 cases only was there any account of tuberculosis in the family, and in but 5 of these cases there was exposure to cases of phthisis possible, while the other 5 were not exposed to family contagion.

The previous history.— Those who reported themselves as being well up to the time of the present illness were 42 in number.

Those who had been sick with other conditions previously to the present attack were 63 in number.

There were 6 cases in which there had been typhoid fever, and in 4 of these, at least, it was reasonable to suppose that the fever had been rather a tubercular fever. Likewise, some of 4 cases of malaria were of doubtful character.

Grippe was spoken of 6 times.

Diarrhea is mentioned as a symptom in 32

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cases, and of these 8 had had this symptom for over one year. Six more had had diarrhea for at least a month before entrance.

In 74 there had been no diarrhea, and 9 of these stated that they were usually constipated.

In the remaining 16 cases no mention of the bowel condition is made.

Hemeter in his report of autopsies on 56 cases of tuberculous enteritis states that in but 2 was there tuberculous peritonitis present.

In the two cases above mentioned when ulcerations were found at autopsy in the intestines there was not a general tuberculous peritonitis present, although other foci of tuberculosis were found in the body. Also in a patient of my own where there was very extensive tuberculous enteritis there was no general deposit of tubercles upon the peritoneum.

In spite of the fact that there was diarrhea present in about one quarter of the cases, it does not seem probable that tuberculous enteritis is an important factor in the production of general tuberculous peritonitis.

Ascites was present in two cases, eight and six years previously, and "peritonitis" once at the age of six months.

Pleurisy was spoken of in 4 cases.

Whooping cough was mentioned 10 times, and in several instances, long duration is mentioned.

In 2 instances a miscarriage was attributed as the starting point.

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One patient was brought to the hospital septic, in the second week after parturition. The peritonitis was found to be due to a tuberculous process.

The *sputum* was examined for the presence of the bacilli of tuberculosis in 24 cases, sometimes repeatedly. The bacilli of tuberculosis were found in but 3 of these cases.

The *stools* were likewise examined seven times, all with negative results.

Leucocytosis.—The white count was 10,000 or less in 58 cases. It was between 10,000 and 14,000 in 21 cases; it was 14,000 in 2 cases; 15,000 in 3 cases, 16,000 in 2 cases, 17,000 in one case, 18,000 in 2 cases, 20,000 in 1 case, 21,000 in 1 case, 22,000 in 2 cases, and in 1 each 27,000, 28,000 and 40,000.

The patient with a 40,000 white count had no fluid, but tuberculous ulcerations in the large intestine and probable secondary infection. The patient with 28,000 had an abscess rapidly develop which brought her to operation; probably a mixed infection. The case with 27,000 had an acute attack of vomiting and diarrhea for several days before the belly had swollen, and is one of the few cases of acute accumulation of fluid which would bear out Murphy's statement that a high leucocyte count is usual in tuberculous peritonitis. One of the 22,000 cases had little fluid but considerable tenderness about the tubes. The other case was that of two weeks' standing and there

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was blood in the stools. The case of 21,000 developed with a chill and the right tube was filled with foul pus; again a secondary infection. The same is true of case with 20,000. Foul pus was also found in one case with 18,000; the other was a child where there was rapid development. The case of 17,000 was one of five months' standing and with probably a general miliary tuberculosis. One of the cases with 16,000 entered the surgical wards with chill and pain in the appendix region, and the other was a case that had been operated upon elsewhere, but had a rapid re-accumulation of free fluid.

Thus, for the most part, the high leucocyte count is accounted for by the presence of septic infection, and, on the whole, the leucocytosis corresponds with the general rule for tuberculosis, namely, a low count.

Onset of symptoms. — There seems to be a general feeling that the symptoms leading to the presence of peritoneal tuberculosis are of an insidious character. The invasion may be unheralded though extensive, but the open outbreak is often sudden and stormy. Gelpke in his recent article states this, though in a note he says that he and others have found that one quarter to one third begin acutely. This coincides with the cases here reported, 36, or 29%, developing suddenly. Bottomley found 13 in his group of 28 cases began acutely, and F. C. Shattuck found 29 of his 98 cases.

Acute symptoms appeared both in the cases

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where fluid was present and where it was absent. In the latter class the symptoms were frequently so acute as to simulate appendicitis, i. e., sudden pain and tenderness localized in the right iliac region, usually accompanied with vomiting. Other cases simulated acute inflammation of the Fallopian tubes. The most interesting group was that where the attack was sharp, with abdominal pain or cramps usually accompanied with vomiting, and within a few days the abdomen became tense with fluid.

A typical account is this: the patient had felt tired for a month, then had a sudden attack of pain and the abdomen three days later was distended. In another there was a sudden pain coming on before breakfast. She was weak and feverish for three days, having a little cough and at the end of that time the belly was found swollen.

Another patient that I had the opportunity to see a few days ago had had pleurisy five years ago, and, five days before I saw her, the belly began to swell and when seen it was distended and tense.

The fact that fluid can accumulate suddenly is not emphasized to any extent, but it certainly should be borne in mind.

In several cases that have been under my observation the converse has been true and fluid has been seen to disappear rapidly, but not so rapidly as it has been said to accumulate. In 2 of the cases who reported themselves as being

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well, both state that they got worse after leaving the hospital when one "took up Christian Science" and another was given "a medicine," and within a couple of weeks' time the fluid had disappeared in each case and they were able to be about again. A third went to his doctor in New York State and was quickly cured. The presence of acute symptoms, therefore, does not militate against the diagnosis of tuberculosis of the peritoneum, and sudden improvement is not rare.

Tubercles.— The extensive distribution of tubercles in most of the cases that were operated upon demonstrated that the disease has been in progress for some time. Two of the cases specially show this; in one, tuberculous peritonitis was unsuspected, but found in the course of an operation for hernia; the other, a longshoreman who fell into the hold of a vessel and who, when operated upon for what was supposed to be the result of his injuries, was found to have extensive tuberculous peritonitis. Neither of these patients had symptoms pointing to this disease. A young girl who was operated upon for appendicitis, having had tuberculous ascites six months before, was found to have her "intestines swathed in tubercles," yet she had been in apparently perfect health for over four months.

These cases go to show that the processes may be present and give no symptom, but that variations in the patient's physical condition may call forth the exudate.

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The peritoneum may have a perfectly typical appearance of tuberculous peritonitis, being everywhere studded with miliary tubercles and have either no fluid at all or have it present in large amounts, and this fluid can accumulate rapidly and also disappear rapidly. All this points to the fact that the ascites is not a symptom to be met with the knife without some special indication for so doing.

Masses.— Indefinite masses were felt in the abdomen in 21 of the cases. This does not include enlarged tubes that were felt by the vagina. These latter were, however, mentioned but three times. The irregular-shaped masses were several times discovered after tapping, and when an operation was performed, were usually found to be rolled up omentum and intestines. Sometimes a very great amount of adherent bowel was found which had given no evidence of its existence from the outside, neither had there been any history of abdominal pain.

Pleuritic effusion.— Evidence of fluid in the chest was found in 19, or 15%, of the cases. In one case there was fluid in both sides of the chest and in the abdomen. A year later, after apparent recovery, fluid reappeared in the left side of the chest, but disappeared again within a few weeks. In another case, mentioned before, but not included in this group of 122 cases, there had been pleurisy with effusion five years before the belly had been attacked.

Fluid in the chest is of no uncommon occur-

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rence, but appears to have no bearing on the prognosis of the case.

Signs of phthisis.— Modification of the normal respiratory signs, all the way from harsh breathing with prolonged expiration to well-marked signs of pleurisy or consolidation, were found 59 times, or 48%, of the 122 cases; that is, abnormalities could be found in the course of the examination of the chest in nearly one half of the cases.

Tuberculin. — The tuberculin reaction was tried in 31 cases; 5 did not react, and in 2 the reaction was of doubtful character, and in one no report was made. Two of the five not reacting were proved to have extensive tuberculous peritonitis at operation. The others were unoperated upon. The tests were usually made by the injection of a single dose of the old tuberculin.

Surgical cases.— In 19 of the 71 surgical cases nothing more was done than to wash out the peritoneal cavity as far as possible with salt solution or to wipe it dry with gauze sponges. In ten more of the cases nothing whatever was attempted more than to look into the abdominal cavity, and then to close the wound again. Adhesions at times prevented the cavity from being opened.

In 4 cases the adhesions were broken up as far as possible.

In 6 cases abscesses or distinct foci of cheesy material were removed. One of these was an external abscess with a deep sinus. In one there

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was a single broken down retroperitoneal gland, and one presented multiple pus pockets among the adherent intestines.

In 5 cases the appendix was removed. In 3 of these there were no tubercles seen on the appendix itself, though there were many in the peritoneal cavity. In another case there was a section of tuberculous gut found while searching for the appendix which was also removed, no mention being made as to its condition. In the fifth case the tip of the appendix was thickened and filled with pus, and on the surface there were a few ulcers. The ascending and transverse colon were also thickened, and the description reads like a case of cecal tuberculosis with involvement of the appendix, rather than a general diffuse tuberculous peritonitis.

In some of the other cases the condition of the appendix was noted as being not abnormal or else tied up in dense adhesions. Nevertheless, only 5 were removed and of those only 1 could be taken as the starting point of the infection and that was not a general infection. In 1 other case where a sinus had persisted after an appendectomy, the secondary operation disclosed a tuberculous lesion at the bottom of the sinus. But here again there was no diffuse process.

Tubes and ovaries. — In 14 cases Fallopian tubes were removed, 11 times both tubes being removed, and in 3 cases only one tube was removed. In 4 cases the ovaries were also excised

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at the same time. The tubes were many times found filled with pus, in some with cheesy débris. In one case where the tubes were practically converted into a cheesy abscess and pus was oozing into the peritoneum, no other tubercles were reported than those in the wall of the tube. In other cases, the interior of the tube was not involved at all although the peritoneal surface was studded with tubercles as was the rest of the peritoneum. There was no case where the condition in any way could be said to be fairly described as a "lupus" of the mucosa.

The tubes may be a source of infection, but it cannot be said that they are the most common source. Rather than any routine removal of the tubes a much more consistent course seems to be to carefully inspect the tubes, and unless specially involved to return them unharmed to their places. In one case where this was done, and although there had been some sharp attacks which would lead one to suppose the tubes were diseased, and the inspection showed that the tubes were somewhat thickened, the patient nevertheless recovered and has remained well and has had no return of discomfort at the menstrual periods which have been regular.

Fluid in the abdominal cavity. — Fluid was reported as present in 84 cases, or nearly 69%. This was demonstrated by operation and tapping 57 times. And also in 22 cases there were undoubted signs of fluid, as shifting dullness, fluid wave, many of the cases having also a dis-

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tended abdomen and protruding navel. In 5 other cases there was but little fluid and possibly some doubt as to its presence.

In 35 cases there was no fluid to be made out by the physical signs (except in two cases where doubtful wave or shifting dullness has been found). This was verified 23 times by operation and once at autopsy.

In the remaining 3 cases there was no record made, or else no definite statement as to the presence or absence of fluid. These are to be included probably among the dry cases, as any amount of fluid would probably have been recognized and recorded.

The amount of the ascites fluid varied from a comparatively few ounces to "several gallons"—10 qt., 8 qt., 10 pt. One patient had 10 qt. withdrawn, again over 8 qt. and 10 qt. more were found at the operation, and a certain amount reappeared after the operation. This patient lived five or six years after the operation. With very few exceptions the fluid found was noted as either clear or yellow, or straw colored. It was reported as purulent 3 times, as cloudy once, as dark once, as bloody once, and in another case blood came towards the end of the tapping when previously it had been clear.

By most authorities the dry cases are supposed to be the least favorable as to prognosis, yet 4 only, or 11%, out of the 35 "dry" cases are on the list of those reported as dead. This makes the deaths among the 84 cases with ascites 33, or 39%.

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Nineteen of the "dry" cases are among those reported living in February, 1908; 13 of these being of the operative cases.

Three more of the "dry" cases heard from at the end of a year, 2 in excellent condition, 1 in poor health and with a cough. These are also operative cases. Three others reporting after the lapse of a year were medical cases. The other 12 cases have not been heard from. In the operative cases the tubes were removed 6 times; twice the appendix was removed, once as being tubercular, the other being chronic appendicitis with tuberculous nodules on the rest of the peritoneum. Twice the operation was for exploration of a sinus and once the draining of a retroperitoneal gland. One other case might be included here when at the first stay at the hospital there was much fluid present, but eight months later when operated upon for an appendicitis there was no fluid in the belly. In the 23 operative "dry" cases there was general tuberculosis of the peritoneum 16 times, and once of the intestine. Certainly this group of cases makes it seem as though the "dry" cases were rather favorable than otherwise. The question naturally arises, What is a "dry" case? or, in other words, may not many of the cases have passed through the active stage like the last patient whom I have mentioned, and become in the process of healing a "dry" case with only the scars and degenerations of the tuberculous process left behind, to be found by the operator? The

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data for the solution of these questions is not at hand.

Tubercles.— Tubercles were found present more or less generally distributed over the parietes, and the peritoneum covering the intestines and pelvic organs in 56, or 78%, of the surgical cases. Of the remainder, in one septic case no note is made. In one case the tubes were mentioned as alone having tubercles and within, the tube was practically a cheesy abscess. In one case the only tuberculous lesion mentioned was the four inches of intestine which was resected. In a number of cases the presence of general distribution of tubercles was not mentioned. Several times the attempt to open the abdomen was futile on account of the dense adhesions, and at others only a pocket was opened, and the general cavity could not be explored.

Adhesions. — In the 71 cases in which the abdomen was examined adhesions were found 54 times while 17 times no mention is made in the records, though from the context their presence may be inferred in at least 3 of these 17 cases. Five of the 17 cases are among those from whom reports have been received. One was the hernia case that had no symptoms of peritonitis and was accidentally discovered and was well when last reported, over four years after the operation. One, also of four years' standing, had both ovaries and tubes and also the appendix removed, and the general tuberculous infection was very extensive. The next case was one in which 4

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in. of gut was excised, and was reported in good condition a year later. A fourth case was one where the abdomen was opened and closed, large-sized tubercles being seen. Still another was one in which a tuberculous sinus persisted in the scar after an operation for appendicitis, and the bowels were found studded with tubercles. One case of seven years' standing had no adhesions. Only one case without adhesions is among the list of dead.

On the other hand, among the patients reporting themselves alive at the time of writing, one, where over four years have passed since the operation, had the intestines bound up into a mass and the pelvis walled off so that the ovaries and tubes were not seen by the operator. A patient, reporting herself in good health, had a tumor which turned out to be a "wab of intestine"; in another, reporting likewise, the intestines were matted together, and still in another of nearly seven years' recovery the intestines were firmly matted together. One case reporting nearly three years after the operation had the intestines and omentum adherent to the pelvic organs.

These are taken as examples of cases with extensive adhesions that have remained well over considerable periods of time and showing that such adhesions may exist without any marked hindrance to general comfort and well being.

Menstruation. — Notes regarding menstrua-

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tion were recorded in the histories of 36 of the women. It was noted as usually regular in 29 cases; irregular in 5, and absent for a space of nine to thirteen months in 2 cases. Several other cases had not menstruated for two or three months before coming under observation. Nine patients had pain at the time of the catamenia and 9 had no dysmenorrhea. In 13 the amount of blood lost was excessive. Three cases out of the 36 had evidently severe disturbance at the time of the menstrual period.

Of the women of whose after history we have any knowledge 8 have reported in regard to their menstruation, and of 4 others inference may be made, two, speaking of themselves in perfect health and two others having been at the out-patient department several times with no record as to dysmenorrhea. One patient, having the ovaries and tubes removed, reported regular catamenia for six months which then stopped; while another, in like condition, reports that she is "all right monthly." One patient where the tubes were covered with tubercles and thickened but were not removed reports her "periods all right." Three only have dysmenorrhea, one, "some pain before catamenia," one, pain and profuse flow one month, the next, normal, and the other, "painful but not much."

Reaccumulation of fluid.—The reappearance of the ascitic exudate after operation is frequent, and according to some surgeons considered practically universal. Gelpke is inclined to ascribe

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to such a reaccumulation the real advantage that may be hoped for by simple operation, on the ground that the new fluid contains active bactericidal properties which make for cure.

Large accumulations do occur after operation, as was seen in one of this series of cases where the patient had been operated upon in Naples, and had had to be tapped two months later and was operated upon a second time having the abdomen again distended with fluid.

Among the operative cases 13 are noted as having a reaccumulation, 18%, a rather small number as compared with the observations of others.

Four cases are recorded as having a large amount reaccumulate, of two small amounts were noted and of the remainder the re-formed exudate probably was not large.

Accidents. — In 3 cases accidents were recorded as taking place during the operation. In one case the cecum which was thickened and tied down by adhesions was opened by the exploring finger. An anastomosis of the intestines was immediately done. There was general tuberculosis of the intestine and peritoneum, and bacilli of tuberculosis were found in the sputum. A letter was returned unopened a year after the operation. Another case where there were dense adhesions, and the ovaries and tubes were removed, the small intestine was torn into in the course of the operation. This patient, though not answering the circular letter recently sent out, was

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alive five years after the operation. The third patient had pain in the region of the appendix, and as the coils of intestines were being pushed aside, one of them ruptured. Four inches of tuberculous gut were resected. This patient, though she had a hard and prolonged recovery, with abscesses and sinuses, was reported at the end of a year in "splendid condition." No report has since been obtained.

Sepsis, abscess and sinus formation after operation. — There are reports of general sepsis, breaking down of wounds, with the formation of sinuses and, in a few instances, of fecal fistulæ, in no less than 19 cases, or 26.7% of those cases operated upon. Four of these cases died while still in the hospital with diffuse sepsis. In 3 of the 4 cases the wounds broke down before death, and in one there was an outbreak of purpura. Deducting these desperate cases from the above 19 cases leaves 15, or 21% of the cases who survived the operation who have had sinuses develop after the operation. In 2 of the cases a fecal fistula formed. In a few cases the sinuses closed before leaving the hospital; others report discharge from the sinus for four months, six months, a year, and one case had a discharging wound for two years, which finally closed after going to Colorado. Still another reports a discharging sinus nearly three years after the operation. In two cases abscess and sinuses did not appear till after leaving the hospital.

In only a few instances is there record of the

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use of any drainage after the operation. The wounds after a varying length of time simply broke down with a resulting sinus. Defect in the catgut is ascribed in one case, but in the light of the general frequency of such results it seems hardly fair to accuse the catgut, especially as the resulting sinus lasted for two years.

To the advocate of operation the danger of a breakdown of the wounds with a sinus and possibly a fistula must be taken into consideration. It has been supposed by some surgeons that the frequency of sinuses after operation for tuberculous peritonitis was confined to the operations of the last century, but the above figures show that the percentage is still high and that operation, even exploratory operation, cannot be advised with the same freedom that is possible in most other abdominal conditions.

Pathological reports. — Pathological reports are found in 38 of the 71 operative cases, or 50%. With two exceptions tuberculosis was demonstrated. In one of these cases where many tubercles were present, the piece removed for examination showed only thickened and hypertrophied tissue. It is evident that no real tubercle was sent to the pathologist. In another case the appendix alone was sent, and this showed no tuberculosis, although there were many tubercles on both the parietal and visceral peritoneum and also on the omentum.

Whenever the tubercles were examined microscopically the typical changes due to tuber-

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culosis were found. The examination of the ordinary macroscopic tubercles in almost every recorded instance, not only here, but in other clinics, gives proof of tuberculosis, and only rarely do cases of pseudo-tuberculosis occur as in the case recently reported by Farrar Cobb, where foreign bodies were found within the tubercles. Cobb, however, makes it plain that pseudo-tuberculosis of the peritoneum is frequent enough to make it practically necessary to clinch the diagnosis in every case with a microscopic examination.

In one case when the microscopic examination showed the typical tubercles the exudate injected into a guinea pig did not kill it. In only a single case were the bacilli of tuberculosis demonstrated in the tubercles.

CONCLUSIONS.

This series of cases presents a number of interesting points.

First, being a general clinic, and drawing from a large and mixed population, the fact that the males and females were in about equal numbers is significant, and is probably nearer to the truth than the figures furnished from the more special clinics.

Second, the onset of symptoms is often sudden and stormy, both in the cases where there is ascitic fluid present and where it is absent.

Third, fluid can go quickly, and improvement take place very rapidly both with and without an operation.

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Fourth, tuberculous peritonitis can be latent, unsuspected, so far as symptoms are concerned, and it can remain apparently unchanged for months after active symptoms have subsided and the patient returned to apparent health.

Fifth, foci for the infection of the general peritoneum have not been found in the Fallopian tubes or in the vermiform appendix in this group of cases.

Sixth, operation should only be undertaken when there is some distinct indication; in the cases with fluid exudate, unless there is distress from the distention, it is better to wait for a period with the patient at rest and under the same hygienic conditions to which any case of pulmonary tuberculosis would naturally be subjected, namely, rest, fresh air, good food and, later, moderate regulated exercise. If after six to eight weeks there is no improvement in the symptoms operation should be considered.

Seventh, the patients, when once the disease is arrested, whether by operation or hygienic methods of treatment, must be taught to regulate their lives with the same care that they would had the disease been located in the lungs.

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ON THE EARLY DIASTOLIC HEART SOUND (THE SO-CALLED THIRD HEART SOUND).

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If one place the hand in the region of the cardiac apex of a young individual with a chest wall not too thick, the systolic impulse of the heart is easily palpable. A slight shock may also be felt at the time of closure of the aortic valves. On auscultation one hears the two heart sounds; the first, more prolonged and low pitched but with a clearly defined ending; the second, short, definite, high pitched, clean cut. In the long pause between the close of the aortic valves and the beginning of the next systole, there is often silence. This, however, is not always the case. As I have already pointed out in another communication,[1] a third sound is not infrequently audible, especially in young people with thin chest walls. The sound is softer and of lower pitch than the second sound; sometimes it is a dull, distant thud; sometimes merely a hum; it occurs shortly after the second sound, that is, at the beginning of the long pause. It is, however, always appreciable at a time later than that occupied by a true reduplication of the second sound, and it is audible only or with greatest intensity at or near the apex. In some

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cases it may be heard over the lower part of the right ventricle. At times, the sound is followed by the faintest suggestion of an echo resembling a slight, early mitral diastolic murmur. This resemblance has, in some cases, been sufficiently striking to suggest that the phenomenon might be due to a similar mechanical cause; so much so, indeed, that I have long been in the habit of maintaining that the entrance of blood from auricle into ventricle is associated in some instances with a slightly audible sound. This early diastolic sound may be associated with a shock which is just perceptible to the palpating hand. The condition is rendered more readily appreciable, and may be brought out in cases in which it is not otherwise audible by a simple manœuvre. If the patient turn well upon the left side in such a position that the chest overhangs the edge of the bed, the apex impulse of the heart which is thrown more directly against the chest wall, becomes more forcible and may be more easily studied by the hand and the stethoscope. On palpation of a heart in this position it is not very uncommon to feel, first, the systolic impulse, then a slight suggestion of the shock accompanying the closure of the aortic valves and second sound, and then, with the relaxation of the ventricle, a third impulse following rather closely after the second sound. In some cases in which an impulse is palpable auscultation reveals no actual well-defined sound. One is, however, sensible of a slight shock to the tympanic

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membrane analogous to that which is felt with the palpating hand. The sound and shock may be more appreciable at the end of expiration.

This sound is certainly not an abnormal phenomenon. It has been familiar to me for over twenty years, and I have frequently mentioned it to my students. It has always been a matter of interest to me that an event so definite, one which must be familiar to many clinicians and physiologists, has not been more generally recognized.

Barié,[2] indeed, in 1893, says: "If one auscult a large number of healthy individuals, one perceives that the long pause is not absolutely free from sound but that there may be heard a slight rudimentary sound, barely perceptible, which if exaggerated will give rise to gallop rhythm." Within the last year the sound has been noted by several observers. Hirschfelder, in an article on "Some Variations in the Form of the Venous Pulse,"[3] describes two cases in which a wave was observed in the jugular pulse immediately after the fall following the so-called *v* wave — i.e., the fall following the opening of the auriculo-ventricular valves — between this and the *a* wave of auricular contraction. In one of these cases, "... the heart sounds were loud and clear, but at the end of expiration a very faint third sound, coinciding with the time noted in protodiastolic gallop rhythm, was audible in the tricuspid area, at the time when the venous pulse was taken. This sound was not loud enough to be definite,

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and none of the tracings which I have made at other times upon cases with gallop rhythm have shown this peculiar variation; so that as yet no definite conclusions as to the relations of this unusual wave of the venous pulse to either the closure of the tricuspid valve or the gallop rhythm are warrantable." Hirschfelder, however, calls attention to the probable correspondence of this wave with the shoulder of the cardioplethysmogram and the time at which the mitral and tricuspid valves are, according to Henderson, closed by the floating together of the cusps.

Recently, an interesting note has appeared by Einthoven,[4] " On a third heart sound." While studying the heart sounds by means of his string galvanometer, Einthoven met with a case in which vibrations were recorded occurring at a period in diastole similar to that in which our sound is audible. These vibrations began on an average 0.13 (.11–.15) second after the beginning of the second sound, and 0.32 second before the beginning of the following first sound, that is, somewhat before the end of the first third of diastole with a pulse rate of 73.

A. J. Gibson,[5] of Oxford, has also observed and well described a similar sound. Gibson's article is interesting, not only because of his excellent description of this sound, but because, although approaching the subject from a somewhat different standpoint, his conclusions as to the probable cause of the phenomenon are similar to ours which were reached quite independently from

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him and before the publication of his article; they are also similar to the explanation hinted at by Hirschfelder. Gibson met with the sound in the course of some studies upon a wave of the jugular pulse similar to that described by Hirschfelder. At approximately the same time at which this wave appears, he detected in two cases, "... a third sound between the second sound and the succeeding first sound. It was heard only at the apex in one, while in the other case it was heard at the apex and over the jugular pulsation in the neck. The sound is by no means easy to hear; extraneous sounds must be eliminated as far as possible and special attention paid to the interval in which the sound is expected. Nor is it possible to hear the sound at every systole; from my own observation it is best heard in the short interval between expiration and inspiration. The quality of the sound is low pitched and clear with no suspicion of harshness or anything suggesting a murmur. Except for the pitch it recalls in type the second sound as heard in fat persons. It is slightly increased in intensity and raised in pitch by pressure on the abdomen."

Our interest in this subject was accentuated in November last in the course of some studies which we were making upon the dog's heart. At this time it was accordingly determined to note all cases in which an early diastolic sound and shock were observed in apparently normal hearts. The results of some of these observations which form the basis of this communication were pre-

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sented before the Æsculapian Club in Boston in December, 1907, but are now published for the first time.

During four months, in the course of ordinary ward visits and in my consulting room, I have met with 24 cases in which an early diastolic sound was heard in an otherwise apparently normal heart.

The condition of the patients at the time of examination was as follows:

Incipient tuberculosis (afebrile),		1
Convalescents, on the eve of discharge from hospital:		
From slight arthritis,	3	8
,, appendicitis (operation),	1	
,, typhoid fever,	2	
,, catarrhal jaundice,	1	
,, obscure hæmaturia,	1	

These patients were, to all intents, healthy individuals.

Healthy individuals, — A physician (Hirschfelder's case),	
A healthy hospital employee in whom the third sound had been discovered while convalescent, some weeks before, from influenza,	
A laboratory assistant in whom the sound was discovered after the man had been used as an example of a normal individual in the preparation of the tracings shown in Fig. 2,	
A healthy boy of fourteen brought to my consulting room by an over-anxious parent,	4

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Cyclic albuminuria, with normal heart and blood pressure,	2
Exophthalmic goitre, a mild incipient case with an apparently normal heart and pulse rate,	1
Chronic tonsillitis,	1
Neurasthenia,	1
Overwork and debility,	1
Chronic appendicitis,	1
Cholelithiasis, in a period of rest,	1
Rather delicate girl with suspected tuberculosis,	1
Nervous, but otherwise healthy boy of fifteen,	1
Chronic adenitis (Hodgkin's disease?),	1
	24

The *ages* of these patients were as follows:

First decade,	1
Second ,,	11
Third ,,	8
Fourth ,,	2
Fifth ,,	2

The youngest individual was five years of age; the oldest, forty-four.

The *pulse*, of normal rate in all cases, tended rather to be slow than rapid; the rate ranged between 50 and 88 to the minute.

The blood pressure was within normal limits in all cases, tending to be rather low than high.

The averages for each decade were as follows:

	Maximum.	Minimum.
First decade,	100–115	(1 case)
Second decade,	106.6 (9 cases)	78.8 (7 cases)

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(In the seven cases in which the minimal pressure was taken the maximal pressure averaged 110.)

Third decade, 114 (8 cases), 77.5 (6 cases)

(In the six cases in which the minimal pressure was taken the average maximal pressure was 119.6.)

Fourth decade, 135 (1 case) 95 (1 case)

Fifth decade, 120 (1 case) 78 (1 case)

In some of these cases the sound was heard only when the patient was lying on his back or on his left side, disappearing in the erect posture. In some it was heard in all postures. In most it was increased in intensity in the left lateral decubitus. In all cases the sound was loudest at the point of maximal impulse in the region of the apex; in several it was heard to a lesser extent over the right ventricle. In none was it audible at the base.

In several cases it was associated with a distinctly palpable shock limited to the point of maximal impulse. This shock was actually visible in a few of these instances. While examining one case in which the third sound was especially clear (the case from which the tracing in Fig. 4 was taken), the stethoscope was handed to a second-year student who had never examined a heart, and was quite unaware of the existing conditions. The student heard the sound and described it accurately.

The early diastolic sound in the dog.— But it is

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not only in the human heart that a sound may be heard at this period. I have three times observed similar sounds in the normal dog's heart. To the first case reference has already been made, — a dog studied with Dr. MacCallum two years ago. In this instance cannulæ had been inserted in the left femoral artery, the appendage of the left auricle and into the peripheral part of a severed branch of the pulmonary artery. By so doing the heart was slightly rotated over toward the right, while the left auricle was held rather tensely in position by the cannula in the auricular appendage. There then became audible in the left auricle and just below the valves a first, second, and then, after a momentary pause, a third sound, a diastolic rumble in every way similar to the early diastolic murmur heard in some cases of mitral stenosis. Gradually the murmur disappeared, and one heard only a thud which became clearer with the decreasing rate of heart's action. One was able to observe systole of the ventricle, immediately followed by the second sound which occurred while the ventricle was still in a state of contraction. Then followed the sudden dilatation of the ventricle which occurred abruptly with a distinct shock, having altogether the appearance of an active muscular process. Synchronously with this shock occurred the third sound, the character of which was precisely that of the sound in protodiastolic gallop rhythm heard under so many circumstances. We were able in this case practically to see the association

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of this sound with a definite moment in the heart's cycle, that is, the shock of what seemed almost like an active diastole.

Since this time Dr. Stewart and I have had two similar experiences. In the first case, at the outset of some observations upon the heart of a small fox terrier, the sounds were found to be perfectly clear. During the process of opening the chest there was an unusual amount of hæmorrhage. When the heart was exposed, with a pulse rate of about 100, a distinct third sound was audible over the left ventricle; it was not heard over the right chamber. This was exactly like the early diastolic sound in the human being, a slight dull thud following the second sound after a period somewhat less than that which separates the first from the second sound. In this instance the dilatation of the ventricle with diastole appeared to be rather rapid but by no means as strikingly so as in the previous case. An attempt was made to study the effects of vagus stimulation. The response was curiously slow and unusual. Stimulation at first produced no result, but, after removing the electrode from the nerve, the heart stopped. With resumption, the first fifteen or twenty beats were very slow, and during these beats, the third sound was more distinct. On large doses of strychnine the heart was seen to draw itself together visibly. The diastolic relaxation was much diminished; the rate rose to about 120; the sound wholly disappeared. Necropsy showed no abnormalities.

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In another dog in which this sound was present, a slight interruption in the dilatation of the ventricles could be seen if one fixed the attention on a bit of epicardial fat on the surface of the right ventricle as it moved under the unopened pericardium. The sound appeared and disappeared at various times during the observation, and the auscultatory changes could always be controlled by the appearance or disappearance of this slight irregularity in diastole. It was evident that the first part of the filling of the ventricle, that before the interruption, was by far the most rapid, and the third sound occurred clearly in association with this rapid filling.

*
* *

How may we account for this early diastolic sound and shock heard and felt so often in human beings and observed in these three instances in dogs? Although during the last twenty years I have often heard the sound in apparently healthy individuals, the explanation of the phenomenon has never seemed clear. Two years ago both Dr. MacCallum and I were struck by its association with what appeared to be a very sudden diastole, so sudden that it seemed to us as if it might almost be an active muscular process, and we asked ourselves whether it might not be a muscular sound due either to active diastole or to the tension of a distended ventricle associated with the sudden entrance of blood from the auricle. The conception of an active

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muscular diastole we may probably dismiss. There is no direct evidence to support the idea.

In considering the cause of this sound and shock in early diastole it may, however, be interesting to inquire into:

(1.) The exact time relations of the sounds.

(2.) The relation of the third sound and shock to the events observed on the cardiogram.

(3.) Their relations to the jugular pulse.

(4.) Their relations to the volume curve of the distending ventricle.

(5.) Their relations to sounds and shocks heard and felt at this period under various pathological conditions.

(1.) *The time relations of the sound.* — As to the first of these points it will be impossible to speak until we shall have obtained a registration of the heart sounds such as is possible only with an instrument analogous to Einthoven's string galvanometer. Einthoven in his case, in which the pulse varied from 73 to 81 to the minute, found that the average time between the beginning of the first and that of the second sound was 0.33 second. The relation of the length of systole to the length of the whole cardiac cycle was as 0.33 : 0.80 or about as 41 : 100. The beginning of the third sound which, it should be remembered, was in this case inaudible, occurred 0.13 second (0.11–0.15) after the beginning of the second sound, and 0.32 before the beginning of the following first sound. The length of the

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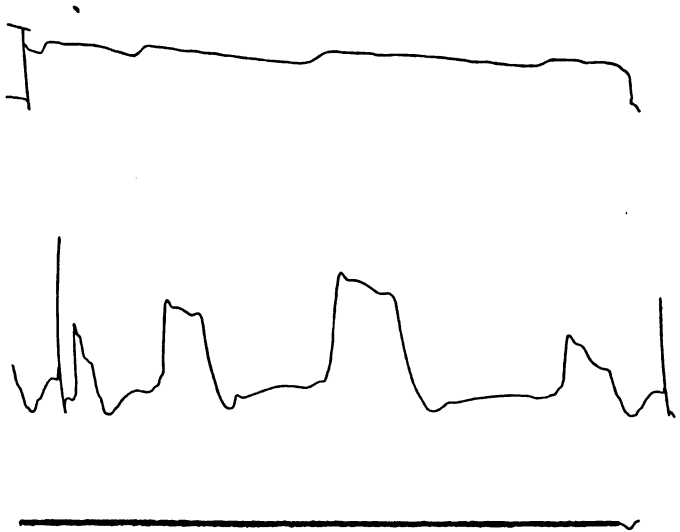

FIG. 1. Normal cardiogram showing protodiastolic and presystolic elevations.

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first sound was 0.08; of the second, 0.05; of the third, 0.02–0.03 second.

(2.) *The relation of the third sound and shock to the events observed on the cardiogram.* — An approximate estimation of the position of the third sound in diastole may be obtained when we take into consideration the events observed upon the cardiogram. If one consider, now, the normal cardiogram, an excellent example of which is shown in Fig. 1, which is reproduced from a tracing taken by my assistant, Dr. Stewart, from a patient with exposed heart from the clinic of Prof. F. Müller, in Munich, it will be seen that there are two slight elevations during diastole, one closely following the katacrotic limb of the systolic elevation, the other preceding the onset of systole. These waves were pictured and described by Marey,[6] who ascribed the early diastolic wave to the influx of blood from the auricle, the presystolic elevation to the increased rapidity of its flow as a result of auricular systole. It is with the early diastolic elevation that we are especially interested. Now in our cases in which an early diastolic sound was heard in apparently normal hearts, this elevation was invariably prominent, so much so that in some cases it could be observed by the hand, the ear and the eye; it was well recorded on the cardiogram in all of 12 cases in which tracings were taken.

As to the relation between the sound and the shock there can be little doubt. They are equally appreciable by the ear and are clearly synchro-

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nous. The comparison of that which one feels, hears and sees with what is registered on the cardiogram can leave no doubt in one's mind that the third sound is closely connected with this early diastolic elevation, and it is difficult to avoid the assumption that the two phenomena are associated with the same causal elements.

At what time in diastole does this elevation occur? In eight tracings from seven cases, the approximate duration of systole estimated by measuring the distance from the onset of the systolic elevation to the shoulder of the cardiogram, was 0.32 second (0.28–0.345). The beginning of the protodiastolic elevation occurred 0.1+ (0.085–0.14) second and the summit 0.18+ second (0.155–0.215) from the shoulder of the cardiogram. The length of diastole, estimated by measuring the period between the shoulder of one systolic elevation and the onset of that succeeding, was, on an average, .594. The average rate in these cases was a little over sixty-five per minute. The sound, then, must occur somewhere within the period occupied by this protodiastolic elevation, between 0.1 and 0.18 second after the end of systole. This is very closely analogous to the time at which Einthoven detected the vibrations in his case, namely, 0.11–0.15 second after the onset of the second sound.

(3.) *The relations of the protodiastolic sound and shock to the jugular pulse.* — Assuming, as we are clearly justified in assuming, that the early diastolic sound is synchronous with the proto-

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diastolic elevation on the cardiogram, we have sought to determine the time of its occurrence on the curve of the jugular pulse. As a result of the study of seven simultaneous cardiographic and venous tracings taken from six individuals, with apparently normal hearts, in whom an early diastolic sound was audible, it has been possible to determine, within fairly definite limits, the events in the venous pulse which correspond to the protodiastolic elevation.

The normal jugular pulse (Figs. 2, 3, 4) shows three marked elevations. The *a* wave which corresponds to the auricular systole, is closely followed by the *c* wave which marks the onset of ventricular systole. The *c* wave is succeeded, during systole, by a deep depression associated with the emptying of the heart and the pulling down of the auriculo-ventricular valves by the papillary muscles. This depression is followed by an abrupt rise, the so-called *v* wave, near the base of the ascending limb of which occurs the closure to the aortic valves. The summit of the *v* wave at which point occurs the opening of the auriculo-ventricular valves, is followed usually by a sharp fall and then a plateau or a slight gradual rise up to the time of the next *a* wave. Other waves may occur during this period. One which has been pointed out especially by Hirschfelder, and subsequently by Gibson, may occur immediately after the depression following the *v* elevation. This has been called by Hirschfelder the *h* wave.

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not the case in the patient from whom the cardiogram in Fig. 6 was taken. It would be well worth while to study the relation in time of the protodiastolic elevation to the shoulder of the cardiogram in a series of cases of mitral stenosis.

(*b*) *Protodiastolic gallop rhythm.* — Potain,[11] fifteen or twenty years ago, pointed out clearly that there were two distinct, principally different, forms of gallop rhythm, the one *presystolic* in time, the other *protodiastolic;* the one associated on the cardiogram, with a wave which immediately precedes the systolic elevation, the other associated with a wave which follows closely upon the base of the katacrotic limb. H. Chauveau [12] and F. Müller [13] have called attention to the fact that "these two points in the diastolic part of the cardiogram in which higher waves are seen in gallop rhythm, are also usually marked on the apex curve of the normal heart by evident but smaller elevations; and one must assume that the larger waves which distinguish the cardiogram of gallop rhythm represent a pathological exaggeration of movements which are also appreciable in the normal heart."[14] Protodiastolic gallop rhythm is observed in some dilated hearts, especially in aortic insufficiency, as well as in certain cases in which there is reason to believe that there are myocardial changes, notably in the course of or just after acute infections, as in typhoid fever.† The third sound occurs shortly

† Further studies as to the relations between presystolic and protodiastolic gallop rhythm, and especially concerning the clinical conditions under which each form occurs, are highly to be desired.

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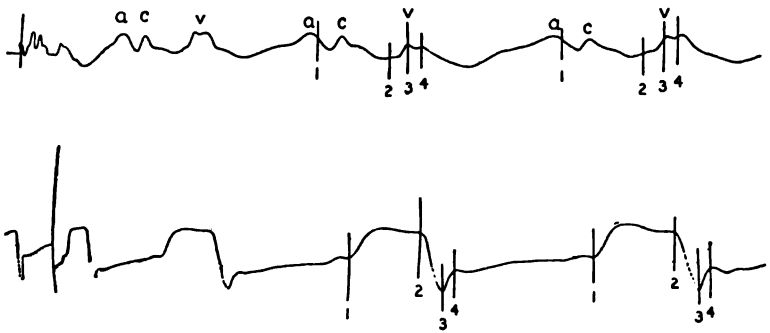

FIG. 7. Cardiogram and jugular tracing from a man about twenty-five, with acute polyarthritis showing a protodiastolic gallop rhythm and shock.

a, *a* wave. *c*, *c* wave. *v*, *v* wave. 1, beginning of systole. 2, approximate end of systole. 3, beginning of early diastolic wave. 4, summit of early diastolic wave.

Transmission time may be estimated by measuring the period between it and the beginning of the *c* wave of a jugular pulse. The *v* wave of this tracing has a peculiar bifid summit. There is no distinct *h* wave.

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after the second at the same period in which the early diastolic sound is sometimes observed in normal hearts. (Fig. 7.)

In *aortic insufficiency* the sound is often associated with a well-marked shock at the apex, a shock which may frequently be accurately timed by placing one hand at the apex of the heart and another over the pulmonic valves. It then becomes possible to make out the 1, 2, 3 rhythm which is audible at the apex: (1) the long, slow, systolic impulse, the so-called *choc en dome*, associated with the dull, humming first sound of aortic insufficiency; (2) the closure of the basic valves, easily felt by the hand in the pulmonic area, which is synchronous with the feeble second sound heard at the apex, and in this area often unaccompanied by the early diastolic murmur audible over the right ventricle, at the base and in the axilla; (3) the sudden relaxation of the ventricle followed rapidly by a definite shock which is coincident with the third sound. In some cases this sound is distinct and well defined; in other instances, dull and thudding. Just about the apex it is often followed, in aortic insufficiency, by the humming, echoing Flint murmur. In the axilla where the Flint murmur, even if present over the ventricle, is often absent, the third sound frequently becomes clear, giving rise to a distinct protodiastolic gallop rhythm. In aortic insufficiency then, the sound varies from a loud echoing rumble to a fairly well defined, short sound or a slight distant hum more appre-

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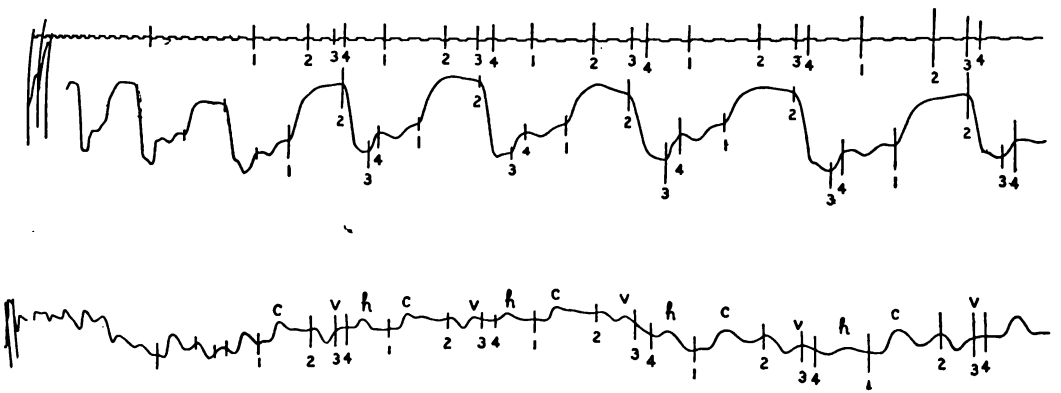

FIG. 8. Cardiogram and jugular tracing from L. B., a man with aortic insufficiency, early diastolic gallop rhythm and Flint murmur.

c, *c* wave. *v*, *v* wave. *h*, *h* wave. 1, the beginning of systole. 2, approximate end of systole. 3, beginning of protodiastolic elevation. 4, summit of protodiastolic elevation.

Transmission time may be approximately estimated by measuring the period between it and the beginning of the *c* wave on the jugular curve.

There is evidently a considerable carotid element in the venous curve.

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have never seen an instance in which *no* further dilatation occurred.

Again, the remarkably small limits of variation in the time at which the normal third sound occurs would tend to suggest that, as Müller and Chauveau hold, it depends on the exaggeration of a normal phenomenon rather than upon causes such as those suggested by Potain.

(2.) Another possibility which presents itself, that which appears to offer the most reasonable explanation, is that with the first inrush of blood, the mitral and tricuspid valves, especially the former, borne up on the entering current toward a position of closure, while the ventricular walls are rapidly dilating, may be brought suddenly into a condition of tension sufficient to cause the sound and shock and to give rise to the centrifugal *h* wave.§

If this hypothesis be correct, one might expect to find the sound more frequent pathologically in cases where, owing to a diminished muscular tonicity, the diastole is more sudden, or where, owing to a weak heart muscle, insufficient emptying of the ventricle and high auricular pressure, such an hypothetical early tension of the mitral valves might be especially favored. But these are, indeed, conditions under which protodiastolic gallop rhythm is common.

Such an hypothesis might well explain its appearance in adherent pericardium where dila-

§ This hypothesis, which, as will be pointed out later on, is essentially that of Gibson, was advanced quite independently of his work and before the appearance of his article.

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tation is so common and diastole notably rapid, because of the traction exercised upon the ventricles by the adhesions.

This explanation also applies peculiarly well to the similar phenomena occurring in aortic insufficiency. Here there is usually a dilated ventricle, often an engorged auricle, as well as the added element of regurgitation from the aorta, conditions peculiarly fitted to produce an early tension and closure of the mitral valves. And here, indeed, the sound is often followed by the slight vibratory murmur (Flint murmur) so analogous to that of mitral stenosis, in all probability due to fluid veins arising in the blood as it passes through the mitral orifice.

It is by exactly the same hypothesis that we have sought to explain the similar sound in mitral stenosis.

If our hypothesis as to the valvular origin of the early diastolic sound be true, one might indeed ask why in cases of dilatation with engorgement of the auricle the valves might not be brought, early in diastole, into a position so analogous to that which they occupy in aortic insufficiency, as to give rise, with the further passage of blood from auricle to ventricle, to fluid veins sufficient to cause a slightly audible diastolic murmur. But this was indeed true in one of our dogs where, at first, the sound was followed by a distinct murmur. Again, as has already been said, the sound in a healthy human being is sometimes a slight hum, somewhat

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longer than the ordinary phenomenon; and indications of such a hum following the sound may sometimes be brought out if the patient turn upon the left side. In adherent pericardium with dilated heart, slight mitral diastolic murmurs without valvular disease have also been described.

Furthermore, I have in one instance met with a third sound, a diastolic murmur in the tricuspid region, which could only be explained by such an hypothesis. The patient was a colored man with arteriosclerosis and dilated heart, but without valvular disease. There was mitral and tricuspid insufficiency due to dilatation of the ventricles. To quote one of my own notes, made in 1905: "In the fifth space, in about the parasternal line, there is heard a distinct mid-diastolic murmur. This begins shortly after the second sound with a slight shock exactly like the opening snap of mitral stenosis, and runs at times almost into the first sound. At other times it stops just before it. It is slightly rumbling and presents all the characteristics of the murmur of mitral stenosis with Flint murmur. It is limited to an area about the size of the bell of a stethoscope. The murmur seems to be more marked during inspiration. No aortic diastolic murmur is to be heard." This murmur, always rather soft, never very intense, was heard throughout the last two years of the patient's life. It was limited to a small area over the right ventricle; never audible at the apex. Its nature was the subject of much discussion, and the only satisfy-

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ing explanation which was reached was that with diastole, owing to the dilatation of the ventricle, the tricuspid valves were brought, with the entrance of the first rush of blood, into a condition of tension causing the sound, and thereafter, owing to the production of a slight *de facto* stenosis, the murmur. At the necropsy, both right and left ventricles were dilated and hypertrophied; there were no valvular lesions. This is the only instance in which I have observed such a shock and sound limited to the right ventricle.

That the phenomenon is due usually to events taking place in the left side of the heart would well explain the fact that the *h* wave of the jugular pulse is so slight in some cases.

This hypothesis is similar to that hinted at by Hirschfelder [17] as an explanation of his *h* wave.‖ Henderson [18] also assumes that the shoulder of the volume curve is associated with the approximation of the mitral valves. Furthermore, the hypothesis is almost exactly that upon which Gibson relies to explain the sound heard in association with his *b* wave. To quote his words: [19] " By observation on the excised heart it can be seen that as the ventricular cavity fills, the auriculo-ventricular valves float up and close automatically when the ventricle is full, and it is easy to imagine that the inrush of blood would be followed by a reaction on the ventricular walls in proportion to the momentum of

‖ Hirschfelder's suggestion, it should be said, relates to the tricuspid, *not* the mitral valve. The principle is, however, the same.

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the inrush, so that with a rapid and full stream the tightening of the valves would be quick and strong while with a slow stream the process would be more gradual yet in no wise less complete. The fact that this explanation necessitates the closure of the valves *before* the auricular beat is no objection; the amount of force necessary to push open the valves is extremely small, and the heart would be the more rather than the less efficient pump because of the double closure of the valves. The sequence of events in the diastolic period would then be as follows: After the replacement of the heart which follows systole and causes the *v* wave in the jugular pulse, the blood flows into the ventricle, the valves float up, gradually when the venous pressure is low, quickly when it is high, and the orifice closes; the auricle is now filled by blood from the veins; it contracts and forces the greater part of its contents into the moderately distended ventricle which then becomes fully so, the valves close again from the increase of pressure set up in the ventricle by the auricular contraction; finally, the ventricular contraction keeps the valves closed till the end of systole."

If this hypothesis be correct, why should the sound be heard in some individuals and not in others, and why should it be especially common in young people? The intensity of the sound is often so slight — so near the borderland of the audible — that it is not remarkable that it is frequently missed. Its apparent frequency in

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individuals with a slow, full pulse would appear to be in accordance with the last mentioned hypothesis, and the observation that the sound is sometimes louder during the slow beats of expiration may well be accounted for by the assumption of a higher auricular pressure during this period.

In connection with the increased intensity of the sound in the left lateral decubitus, it should be noted that, in this position, a well-marked systolic apical murmur may be brought out in cases where, in other attitudes, the heart sounds are clear. If this murmur be regarded as indicative of a functional insufficiency of the mitral valve, the third sound may then well be dependent on the more sudden distention of the ventricle with an increased quantity of blood under higher pressure.

There would, however, seem to be no reason to suppose the existence of especially high auricular pressure or of diminished cardiac tonicity in the many healthy young people in whom the sound is heard. I have always fancied that one, if not the main, reason that the sound was so well heard in the young was because of the thinner chest walls, the less voluminous lungs, and the greater ease with which the heart can be approached.

(3.) There is another possibility with regard to the cause of this sound which may be simply mentioned. Stewart has shown that there is in the normal heart an early diastolic contraction

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of the ring of muscle just below the aortic and pulmonic valves, a contraction which serves evidently to reinforce the closure of the arterial orifices. His work has not yet been published, and while one might *a priori* expect that the sound associated with such a contraction, if such a sound indeed there be, would occur at a somewhat earlier period, and that it would be more appreciable at the base of the heart than at the apex, yet in the absence of positive proof of that which we have advanced as the most engaging hypothesis, it may be well to bear in mind the possibility that the contraction of the aortic ring may be a factor in the production of the sound, however improbable it may seem.

SUMMARY.

In many healthy individuals, especially in the young, there is audible at the apex of the heart a slight third sound, which occurs in early diastole shortly after the second sound.

This sound is commoner with a slow pulse; it is better heard in the recumbent posture and, especially, in the left lateral decubitus. It is sometimes more clearly audible during expiration.

The sound is not infrequently associated with a shock which may be visible as well as palpable. The sound and shock occur synchronously with the protodiastolic elevation of the cardiogram which is usually prominent in these cases.

These events cover a period of time represented on the jugular pulse by the later part of the kata-

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crotic limb of the *v* wave and, generally, a part of the anacrotic limb of an *h* (Hirschfelder) wave (*b* wave of Gibson), which is usually present in these cases. This period corresponds closely to that occupied by the shoulder of the ascending limb of the cardioplethysmogram.

Conclusive evidence as to the cause of this phenomenon is, as yet, wanting.

From a consideration of the conditions observed in normal individuals, together with various apparently analogous manifestations occurring in disease, we are disposed to incline toward the hypothesis that the sound is produced by a sudden tension of the mitral and, perhaps at times, tricuspid valves occurring at the end of the first and most rapid phase of diastole.

In conclusion I wish particularly to thank my friend, Dr. Eyster, of the Physiological Department, for valuable assistance.

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THE VALUE OF LUMBAR PUNCTURE IN SYPHILITIC AND PARASYPHILITIC DISEASES OF THE NERVOUS SYSTEM.

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IT is now seven years since Monod,[1] working in Brissaud's clinic, and Widal, Sicard and Ravaut [2] called attention to the fact that an increase of lymphocytes in the cerebrospinal fluid of individuals suffering from general paresis and tabes is almost constantly to be found. Following the work of these pioneers a large number of papers have been published, mostly by French and German investigators, corroborative of their work. Besides the increase in lymphocytes, it has been repeatedly demonstrated that serum albumin, which exists not at all or in only slight traces in normal cerebrospinal fluid, is increased in tabes and paresis to from 2 to 4 gm. per thousand.

It is not from lack of appreciation of the constancy of this albumin increase that the writer has omitted this test in many of his cases, but because its performance requires a larger amount of fluid than does the cell count. The fact that all the cases reported in this paper were tested either in the office or in the out-patient clinic rendered it inadvisable to withdraw more fluid than was

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necessary in order to obviate the development of uncomfortable symptoms which sometimes follow the operation. Moreover, the proteid estimation, while in itself of value, gives little additional information if the cell count is to be made. It is true that a few cases have been reported where the albumin test was positive and the cell count negative, but in these cases the cell count was made by the old method which lacks the accuracy of our present method of estimation.

As a matter of fact, we know that the number of cases of paresis in which the cell count has failed to show a lymphocytosis is very small. Pomeroy [3] has collected statistics of 500 cases suffering from this disease in which lumbar puncture was performed, and only 2.6% gave a negative result. Cornell, who used the more accurate slide counting method, has had no negative counts in 37 punctures, while Fuchs and Rosenthal [4] had 12 and Rhems [5] had 39 without a negative result. Based on these data, Cornell [6] gives it as his opinion that every case of paresis shows a cellular increase in the cerebrospinal fluid.

Regarding the constancy of the sign in tabes, Fuchs and Rosenthal collected 154 cases in which the sign was positive and 13 in which it was negative, while in their own tabetic case it was positive. Purves Stewart [7] found 8 cases positive and reported 1 case of his own of undoubted tabes in which the count was negative and referred to a negative case of Ferrier and Babinski.

In the light of all that has been done, therefore,

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we must accept the fact that a leucocytosis of the cerebrospinal fluid is practically always present in tabes and general paresis, and Joffroy,[8] as well as Marie and Duflos,[9] maintain that it is present in the earliest stages.

The value of this aid to diagnosis has been made use of by some in cases of tabes, but to a much greater extent by psychiatrists in differentiating general paresis from psychoses which may simulate this disease, notably alcoholic psychoses, arteriosclerotic psychoses, dementia precox and psychoneuroses.

The object of this communication is to show by brief abstracts of a few records the sort of cases in which lumbar puncture is useful to the practitioner; to add my endorsement to that of the advocates of the slide counting method; and to call attention to the fact that the test can be made in the office or in the bustle of an out-patient clinic and the results obtained in a few minutes.

I am aware that Pomeroy and Nissl[10] make as their first rule: "Patients should not be punctured unless they can be put to bed." It is here, however, that the advantage of making the count without the corroborative evidence of the albumin test is manifest, for if done by the slide counting method, only a few drops of the fluid are needed, and the occasional results of headache, nausea and malaise may be avoided.

The method of procedure of nearly all the investigators who have employed cytodiagnosis of the cerebrospinal fluid has been to collect the

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fluid in a conical-shaped tube and centrifugalize it at a high rate of speed for twenty to thirty minutes. The fluid is then poured off and the tube inverted and allowed to drain until only a small drop remains in the small tipped end. This drop is absorbed by means of a fine capillary pipette and is spread on three coverslips, dried, fixed and stained. The count is then made with a 1-12-in. oil immersion lens and the average number found in a field is estimated.

The results obtained by this method must vary with the time and rapidity of centrifugalization and the technique of the investigator, for it is obvious that the varying size of the drop left in the tube and the character of the spread must give rise to widely different results.

We owe to Fuchs and Rosenthal the introduction of a modification of the Thoma Zeiss blood-counting apparatus, as a more accurate means of estimating the number of cells. They employed the white blood corpuscle counter, drawing a staining mixture up to 0.5 and filling the tube to 11 with the cerebrospinal fluid. For the purpose of staining they used methylene violet 0.1, acetic acid 2, and water 50, which mixture serves to bring out the character of the cells and distinguishes the red corpuscles which may contaminate the fluid. When the fluid has been thoroughly mixed and stained, the count is made on a slide which differs from the ordinary blood counting slide in that the chamber is larger, measuring 4 mm. square and 2 mm. deep. By counting two or three spreads

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on such a slide the average is taken and the number of cells per cubic millimeter easily computed.

It has not seemed to me necessary to use the modification of Fuchs and Rosenthal, for in making the count on the ordinary blood-counting slide I have found that if the fluid be well mixed in the pipette that there is very little variation in the count of four or five successive preparations. If the validity of the count is corroborated in this manner the number of cells per cubic millimeter is easily estimated.

The value of this method of counting lies chiefly in its accuracy, allowing the results of one investigator to be compared with those of another without question of any variation depending on technic. In this way it may be possible by collecting a large number of cases to make finer distinctions between a number of conditions in which lymphocytosis has been found, and we do not need to deal with such terms as "positive results," "moderate increase," and "marked increase."

All the evidence goes to show that the normal fluid by the old method of counting demonstrated from no cells to two cells in a field, and by the new method from no cells to three cells in a cubic millimeter. There is nearly always a moderate or marked increase in the number of cells in cases of (1) syphilis with active secondary lesions; (2) syphilis of the central nervous system; (3) syphilitic eye disturbances; (4) tabes; (5) general paresis; (6) tubercular meningitis. In addition

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to these an increase may be found in (1) multiple sclerosis; (2) mumps; (3) herpes zoster.

There is little difficulty in making the diagnosis from the clinical picture in this latter group of cases, and this is true also of the secondary stage of syphilis and of tubercular meningitis. The real value of the lymphocyte count lies (1) in those cases where there is a well-developed psychosis in which paresis is to be differentiated from other psychoses; (2) in patients who show beginning changes in character and disposition, where the question of a possible early stage of paresis is suggested; (3) patients having isolated symptoms of tabes, such as retention of urine, paresthesiæ, pains, or crises, but who do not show a sufficient number of characteristic symptoms to make the diagnosis of tabes certain; (4) in differentiating cerebral tumors from gummatous growths.

In the light of our present knowledge, however, where the alternative of syphilis of the brain or cord comes up in diagnosticating paresis and tabes, we cannot depend on the lymphocyte count as an aid, for the cell increase is quite as constant in the syphilitic as in the parasyphilitic affections of the nervous system.

It is true that Stewart, in using the cell-counting slide, believes that the average count in syphilis is lower than that in tabes and paresis, giving as his results:

Syphilis,	7	cases, average	37.6	per cmm.
Tabes,	8	,, ,,	72.3	,,
Paresis,	4	,, ,,	190.4	,,

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The average of 190 in paresis, however, is much higher than Cornell reports, for he found that as a result of lumbar puncture 37 times in 25 cases of paresis that the average number of cells was 52, the individual counts varying from 12 to 216. It is apparent from these figures, therefore, that cytodiagnosis can be of no assistance in differentiating tabes or paresis from syphilis in cases where the count is in the vicinity of 40 or 50.

During the past year I have used lumbar puncture as a means of diagnosis in 30 cases; in only 3 was the operation really painful, and in only 1 were there any unpleasant after-effects. This was due to the fact that the fluid was under such pressure that an unusual amount escaped before the needle was withdrawn. The result was that the man was confined to bed for a week on account of headache and malaise. In many instances the patients went considerable distance to their homes after the operation (Lawrence, Lynn, Lowell, etc.) and no discomfort was felt.

It is surprising how little pain is caused by the introduction of the needle in most of the cases. After scrubbing the lumbar region with soap and water and alcohol, local anesthesia was produced by means of the ethyl chloride spray, and several times the patient has remarked that the introduction of the needle was much less uncomfortable than the rubbing of the towel.

The outlines of the following selected records serve to illustrate the type of case in which the leucocyte count of the cerebro-

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spinal fluid is of value as an aid to the diagnosis. In all of the cases the number of polymorphonuclear cells has been below 5%, but since these are always present in some degree, I have made use of the word "leucocytosis" rather than "lymphocytosis" to express the cellular increase.

Case I. Male, thirty-two years of age. Came to Out-Patient Department of the Massachusetts General Hospital on account of retention of urine. Two years previously he had begun to have difficulty in micturition, and this had increased so that he had been obliged to use a catheter for several months previous to his first visit to the hospital. He had contracted gonorrhea four years previously, but denied knowledge of having had syphilis.

The pupils were equal in size, slightly irregular in outline, and reacted well with accommodation, but not to light. The knee jerks and Achilles reflexes were present. There was no ataxia or Romberg's sign, and no history of darting pains or paresthesia.

The Argyll-Robertson pupil in this case suggests tabes as a cause for the bladder symptoms. This diagnosis could not have been made with certainty, however, without the aid of lumbar puncture, which showed 110 leucocytes per cubic millimeters corroborating the diagnosis.

Case II. A man thirty-four years old gave a history of having contracted syphilis eight years ago. He came to the hospital in February, 1907, on account of Jacksonian attacks, from which he had been suffering for several months. The attacks were ushered in by an aura of a sense of tightness, starting in the toes of the

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left foot and extending up the leg. There was then a tonic spasm of the leg followed by unconsciousness and clonic spasm of the left half of the body. There was no headache or vomiting and no optic neuritis. No history of trauma. The pupils were irregular in outline, the right 4½ mm., and the left 2½ mm. in diameter. Both pupils reacted well with accommodation, but the left reacted sluggishly and the right not at all to light. The left knee jerk was more active than the right and there was ankle clonus on the left side. Sensation was normal in all its forms. There was no tremor of the lips or tongue. The speech was not suggestive of paresis, nor was there the characteristic mental indifference and memory defect of this condition.

The question arose as to whether the symptoms were due to cerebral syphilis or tumor of the brain in the region of the precentral convolution. A lymphocyte count of 35 made it possible to rule out the latter condition and accept the former, although the possibility of the convulsions being an early manifestation of paresis was recognized. As a matter of fact, the attacks have now been absent for a year under a thorough iodide treatment, and the patient has showed no further signs of paresis.

CASE III was that of a man forty-two years old, who had contracted gonorrhea at the age of twenty, but gave no history of having had syphilis. In August, 1907, he ran to catch a car, mounted the running board and stood for a moment, when he suddenly had a sensation of having been struck in the left knee, and knew no more till he came to himself in the hospital. During

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the next two months he had attacks of Jacksonian convulsions involving the left side, at intervals of one or two weeks. In some of these he retained his consciousness, and others were observed by attendants. The attacks were ushered in by the left leg drawing up, and a few seconds later a clonic spasm of the left arm. In the course of a few weeks there developed weakness of the left arm and leg, so that he found great difficulty in walking and dressing. There was a moderate degree of headache, but no vomiting. The intellect was clear. Pupils equal and reacted promptly. No optic neuritis. No signs of involvement of cranial nerves. Marked paresis of left arm and leg. The left knee jerk was more active than the right, but there was no ankle clonus. The superficial reflexes were absent on the left side.

Here, as in Case II, we have to differentiate between a localized syphilitic process in the brain and a developing neoplasm in the region of the motor cortex. Examination of the cerebrospinal fluid showed but one cell per cubic millimeter which supported the diagnosis of tumor, and operation was advised, but declined by the patient. Iodide of potassium in doses of 200 to 300 gr. a day were given for several weeks in the forlorn hope that some relief might result, but no improvement has manifested itself in the course of three months.

Case IV was a man of fifty-six, seen with Dr. J. J. Putnam in the fall of 1907. For a year past the patient had been unable to attend to his work of auditing accounts because of his feeling of mental incapacity. He had three distinct complaints: (1) in walking he felt as if some one were pulling down on his legs so it was

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hard for him to lift them from the ground; (2) in conversation he was apt to think the first half of what he intended to say and begin talking in the middle of a sentence, and while talking he found it a distinct effort to get his tongue around words. His wife also said that he had a recent habit of leaving his sentences unfinished. (3) He was occasionally overcome with dizziness when things seemed to be blurred and move in front of him, and he was in constant fear lest such an attack seize him in the street.

He denied having had syphilis and used alcohol very moderately. Physical examination showed a stout, muscular man, well preserved for his years. He was very talkative and the speech was somewhat slurring. His conversation and manner were both very suggestive of general paresis. He repeated phrases correctly, however, and was quick and accurate in multiplying figures. There were no grandiose ideas. The pupils were regular, equal and reacted well. The fundus was normal. The tongue and lips showed no tremor. The knee jerks were normal. The examination of the cerebrospinal fluid showed one leucocyte per cubic millimeter.

Although there were no somatic signs of general paresis in the patient, and the leucocyte count was normal, his manner seemed so convincingly that of a paretic that a second puncture was performed two weeks later, but the fluid showed only two cells per cubic millimeter. Relying on the cytodiagnosis in this case it is possible to rule out the diagnosis of paresis, and we are forced to accept either a psychoneurosis or an arteriosclerosis as a cause for the condition.

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Body, that of a man about thirty years of age; length 155 cm.; fairly well developed and nourished; rigor mortis absent; body warm; slight lividity of dependent parts; pupils equal, 3 cm. in diameter; the skin a general deep yellow color; the skin of the middle of the forehead shows an old, slightly depressed scar, 2 cm. in diameter; the skin of the body and extremities bears numerous irregularly oval, shallow, white scars, the largest about 1 cm. across.

Upon section, subcutaneous fat 1 cm. in thickness, muscles red and firm; vermiform appendix and mesenteric lymph nodes normal.

Thorax, height of diaphragm fourth rib on right side, fifth rib on left.

Pleural cavities, normal.

Pericardial cavity, normal.

Heart, section of the vena cava and pulmonary veins yields dark fluid blood. Weight 270 gm.; myocardium brownish red, microscopically showing interstitial fat; wall of left ventricle 1.3, of right, .3 cm. in thickness; mitral valve 10, aortic valve, 6, pulmonary valve 6.5, tricuspid valve 12 cm. in circumference, depth of left ventricle 8.5 cm. Endocardium, valves and cavities normal. Coronary arteries normal.

Lungs, normal.

Abdomen, peritoneal cavity normal.

Spleen, weight 100 gm.; upon section, dark red, markings distinct; pulp not increased; consistence a little diminished.

Stomach, normal.

Intestines, small; the ileum shows several small areas of hemorrhage in the mucosa, otherwise intestinal tract negative.

Pancreas, normal.

Liver, weight 730 gm.; symmetrically diminished in

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size; length, 19.5, breadth 13 cm., lower border 6 cm. above the costal margin, lay high up under the diaphragm and rather far back; flaccid, flattening out when placed on a table; general color brown red; the free surface in general smooth, presenting here and there areas of varying size, the largest about 2 cm. across, slightly elevated and of a greenish color; upon section, the general cut surface brownish red; devoid of lobular markings, presenting an even, fleshy appearance; distributed over the surface are areas corresponding in size and appearance with those upon the free surface, slightly elevated, firmer than the surrounding liver substance, showing distinct lobular markings; the centers of the lobules bile stained, the borders yellowish brown. The hepatic veins stand open, the surface of section is moist.

The microscopical examination is as follows: In this liver there are two different conditions which are separated, both macroscopically and microscopically. In certain areas, there is a comparatively large amount of well preserved liver tissue. Liver cells are normal. The nuclei stain well and the fine bile capillaries between the cells are injected with a greenish yellow bile pigment. These areas in the liver macroscopically appeared greenish. The liver cells contain no fat and the nuclei are relatively more numerous. There seems to have been a new formation of liver cells. The trabeculæ are wider than normal in places. The capillary bile ducts are dilated. No nuclear figures are found in the liver cells. The preserved liver tissue is chiefly about the portal spaces. The connective tissue in the portal spaces is increased. About the central veins everywhere the liver tissue is absent. In other sections which involve rather the less pigmented areas macroscopically the liver cells are in places

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entirely absent or reduced to very small cell collections. One of the most marked features where the liver cells are absent is the presence of immense numbers of endothelial cells. These cells have an abundant dense cytoplasm, are often pigmented, are contained both within the capillaries and within the liver cell trabeculæ, and sometimes show vacuoles containing granular material or pigment. Where the liver cells are absent the tissue consists in a loose fibrous stroma containing these cells with some admixture of lymphoid cells. Here and there the endothelial cells contain lymphoid cells within their vacuoles. In many of these places there are a few scattered eosinophile leucocytes. In a few places only at the edge of the liver cell masses, the same process of cell disintegration, which is fully described in the other cases, is seen. The portal spaces and the tissue adjoining them everywhere contain immense numbers of the so-called newly formed bile ducts. In places, particularly where the liver cells have totally disappeared, these are very prominent and penetrate the tissue. They seem to be actively growing, the nuclei are numerous and nuclear figures in fair numbers are found in them. This case differs from the two following cases in the fact that here a destructive process analogous to that in the other cases, though not so extensive, has taken place. The period of destruction has ceased, or almost entirely so, and the dominant feature is a repair of the process, and regeneration. The regeneration of the liver tissue here is taking place in two ways: in one way by the direct formation of liver cells from other liver cells by division of nuclei. In the other, by a process similar to that of embryonic liver formation, by the formation of undifferentiated epithelial tissue similar in character to the bile ducts, from which the future liver cells will differentiate.

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and with greenish pigment are numerous. Among these there are often larger cells which show active phagocytosis. One of the most striking conditions in this case is the complete absence of polynuclear leucocytes.

The condition in this liver is one of intense destruction of liver tissue. The condition is different from that which is seen in the ordinary necrosis of liver cells. The cells seem to soften and disappear by solution, leaving in some cases a more or less granular-looking mass behind. The condition affects also the capillaries of the liver. In the place of the liver tissue there is beginning to form a tissue composed chiefly of endothelial cells which in a few places show an active phagocytosis. The same process of tissue solution has affected the blood as there are no blood corpuscles in the most marked areas. In this softened tissue in places there has come a fresh influx of blood, the blood corpuscles lying chiefly in the spaces formerly occupied by the rows of liver cells. There is in no place any indication of regenerative process.

Kidneys: weight, 370 gm. Capsule strips readily from a smooth surface. Cortex well differentiated. Pyramids 7–10 mm. in thickness. Color grayish red. Glomeruli can be seen as gray points. Pyramids dark red. Blood vessels seen as reddish lines.

Scharlach R. shows fat in small droplets, large in quantity, within cells lining tubules of cortex and pyramids.

Adrenals are somewhat thin. The left adrenal seems lumpy. No gross lesions can be determined. Scharlach R. shows fat in central zone of cortex and in cells lining medullary portion.

Bladder and *genital organs* seem normal.

Aorta shows a moderate grade of fibrous sclerosis

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running in longitudinal lines along the posterior wall.

Organs of neck.— The thyroid seems normal in size and consistency.

Lymph nodes.— The inguinal lymph nodes are somewhat enlarged. On section several of them show pinpoint yellowish-white firm spots. The mesenteric lymph nodes about the bile ducts and head of the pancreas are markedly enlarged and dark red on section. The post-peritoneal lymph nodes and the mesenteric lymph nodes in general are appreciably enlarged, on section dark red. Several of the mesenteric lymph nodes are calcareous.

Bone marrow.— The shaft and head of the right femur is rather gelatinous and alternates streaks of yellow with streaks of dark red.

Head.— Short, curly, dark brown hair. Scalp and calvarium of normal thickness. Dura non-adherent. Sinuses contain fluid blood. Pacchionian granulations moderate. Some little subpial edema. Vessels of pia injected. Circle of Willis normal.

Brain: weight, 1,380 gm. Rather firm in consistence. Convolutions of normal prominence. Ventricles, midbrain, pons, medulla and basal ganglia show nothing of special note.

Chemical examination of liver and intestinal contents. — The contents of the jejunum, ileum and colon were examined thoroughly and repeatedly for phosphorus without finding any.

The liver in this case was examined chemically by Dr. Carl S. Alsberg. It was slightly richer in water than is normally the case. It also contained a greater per cent of ether extract than is normally present, but as the liver weighed only 600 gm., the total ether extract of the entire liver was very much less than the ether

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extract of a normal liver of 1,800 gm. In other words, while the relative amount of fat and lipoids was somewhat greater than normal, the absolute amount was very much less than normal. Furthermore, the nitrogen distribution was determined according to the method of Hauseman, Osborne's modification. The nitrogen precipitable by phosphotungstic acid was diminished and the nitrogen not precipitable by this reagent very markedly increased. These are conditions which very clearly show marked autolysis.

Case III. M. C. C., age thirty-six, married, born in Ireland, a housewife, was admitted to the wards of the Boston City Hospital in the service of Dr. Francis H. Williams, on Dec. 1, 1905. Through his kindness the writer was permitted to examine and study this patient. The history was obtained from her physician and husband. Her family history was excellent. She had always been strong and well, no previous illnesses were remembered. Had used no alcohol and syphilis was denied. Two children had died soon after birth, of digestive disease; no miscarriages. Her digestion had been excellent and she had had no disease of the genital organs. There had been no recent infectious disease.

Present illness. — This began six days previous with severe headache, anorexia, malaise and general weakness, accompanied by a moderate flow of blood from the uterus. The last catamenia had ceased one week before; they had previously been very regular.

She had been in bed since the second day of the illness. There had been diffuse abdominal pain, occasional vomiting, and the bowels moved on the fifth day for the first time in several days. On the fifth day several mouthfuls of blood were vomited and slight jaundice was noticed for the first time. On the sixth day (the day of entrance to the hospital) the patient

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became drowsy and lost consciousness for the first time. At entrance to the hospital she was semi-conscious, could only be roused by the strongest external stimuli,would not answer questions,rolled about the bed.

Physical examination showed a well developed, poorly nourished woman whose skin and conjunctivæ showed slight jaundice. The skin was very dry and scaling in several places on the abdomen; the tongue had a dry brown coat; the odor of the breath suggested acetone. The glands were not enlarged, neck not rigid or tender. The pulse was regular, slow, of good volume and tension. The heart was normal in size and the apex palpable and visible in the fifth space within the nipple line. The action was regular, both sounds were sharp and loud and the first sound reduplicated at the apex. A slight systolic murmur was heard at times at the apex and a cardio-respiratory murmur just to the left of the nipple. The lungs were normal. The abdomen was soft and lax without tenderness, masses or fluid. The *liver dullness* was difficult to determine accurately. There was tympany instead of flatness in the upper epigastrium and in the nipple line. The only definite area of dullness found was in the right axilla between the seventh rib and the costal margin extending only as far forward as the anterior axillary line. The spleen was not felt, nor the dullness found to be enlarged. The reflexes were normal. Kernig's and Babinski's sign were absent. The temperature was normal.

The blood on the sixth day was, hemoglobin, 60%; red cells, 6,720,000; white cells, 16,000.

The urine on the same day was passed involuntarily so that the twenty-four-hour amount could not be collected. A mixture of several catheter specimens showed the following characters:

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Reaction acid; specific gravity, 1,028; color normal; albumin, a very slight trace; sugar absent. Albumose present; bile pigment present in small amount.

The sediment contained a few coarse, granular casts and renal cells with fat drops, a little free fat, leucocytes and squamous cells. Calcium oxalate crystals.

On evaporating the urine and precipitating with alcohol, both leucin and tyrosin were found present.

Quantitative analysis of the nitrogen excretion made by the writer showed that 69.2% was excreted as urea, 17.0% as ammonia; 13.8% as residual nitrogen including uric acid.

The stools were formed, of very dark color and contained a considerable amount of partially digested blood.

The treatment was essentially symptomatic. Purgation with calomel, with large enemata of salt solution; bromides for the restlessness, and heart stimulants. During the afternoon of the sixth day the patient's condition remained unchanged. She was very restless and noisy, tossing about in bed, rolling her head incessantly from side to side. There was no more vomiting. The patient occasionally coughed up a little blood-streaked sputum. A moderate bloody discharge from the uterus continued. The jaundice gradually deepened to a yellowish bronze color; the conjunctivæ were bright yellow. There were no hemorrhages into the skin. The bowels did not move again. Profound coma gradually developed. There were no convulsions, twitching, or rigidity. The temperature remained normal. The pulse became rapid and gradually failed. The patient died at noon on the seventh day of her illness and the second day after the appearance of jaundice.

The *autopsy* was performed by Drs. Mallory and

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Graham of the Boston City Hospital, twenty-two hours after death.

Anatomical diagnosis:— Acute yellow atrophyof liver; acute parenchymatous nephritis; acute myocarditis; generalized icterus of skin, subcutaneous fat and serous membranes; multiple hemorrhages of lungs; multiple hemorrhages of mesentery; hemorrhages from gastric and intestinal mucous membranes and endometrium; congestion and edema of lungs; chronic pleuritis (bilateral); chronic perihepatitis; generalized passive congestion; myoma of uterus; biliary calculus; aortic arteriosclerosis (slight).

Body of a well developed, fairly nourished white woman, 159 cm. in length. Rigor slight in limbs, absent in neck muscles. Lividity of dependent parts marked. No edema. There is general icterus, skin surfaces a yellowish bronze in color, sclerotics bright yellow. Pupils equal, 0.5 cm. in diameter.

Peritoneal cavity. — Subcutaneous fat is of a salmon yellow color, its vessels filled with dark blood. Pectoral muscles dull red. On opening cavity all the serous membranes show yellowish discoloration. The mesentery shows numerous scattered punctate hemorrhages beneath the serosa. They occur in the region of the vasa intestini tenuis, especially along the line of attachment of mesentery to intestine and average 0.2–0.3 mm. in diameter. They are most numerous in the region of the small intestine. Appendix 7.5 cm. long, 0.6 cm. in diameter; direction downward and inward. Mesenteric lymph nodes not enlarged. Diaphragm, right fifth space, left sixth rib. No fluid.

Pleural cavities.— There are old fibrous adhesions over surfaces of left lung posteriorly; over surface of right lung anteriorly. No fluid.

Pericardial cavity. — Serosa smooth, glistening

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throughout. Cavity contains about 25 ccm. of clear, dark yellow serous fluid.

Heart: weight, 245 gm. Pericardium smooth. Myocardium dull red, flabby; on section shows vaguely marked areas of opaque yellowish gray color; appears loose in texture. Endocardium shows yellowish discoloration. Coronary arteries not sclerosed. Valves negative.

Scharlach R. shows throughout the entire section the muscle fibers crowded with small fat droplets; large flat cells occur in the fibrous trabeculæ.

Lungs, right: middle lobe pinkish, crepitant; on section dry. Upper and lower lobes show slightly marked congestion and edema. Throughout both these lobes there are numerous scattered areas of hemorrhage averaging 0.5–1 cm. in diameter, which are most numerous in dependent portions. Anterior surfaces show tags of fibrous adhesions.

Left: Upper and lower lobes reddish in color, crepitant. Tags of fibrous adhesions posteriorly. On section, color bright red, surfaces are moist and show multiple hemorrhagic areas, especially posteriorly and inferiorly. There is no evidence of pus formation.

Spleen: weight, 100 gm. Capsule lax; on section, cut surfaces dull red in color, mottled with clearly defined grayish areas averaging 1 mm. in diameter. Trabeculæ distinct. Little pulp on scraping.

Gastro-intestinal tract. — Stomach shows adherent to mucosa a few small scattered, reddish-black masses appearing like old blood clots. Mucosa not perceptibly congested. The jejunum is empty except for a considerable quantity of reddish-black mucoid material with slight fecal odor. This material shows, microscopically, the presence of red blood cells in considerable

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quantity. Similar material is found in the cecal region. No bleeding points found.

Pancreas. — Organ is softened in consistence. Cut surfaces moist and of edematous, semi-translucent appearance. Color dull grayish white. The spaces between the groups of gland acini are hemorrhagic.

Scharlach R., shows large fat droplets in the inter- and intra-acinar connective tissue. The parenchymal cells show a slight fatty change.

Liver: weight, 960 gm. On opening the abdominal cavity, liver appears to have fallen back from its normal position on to the posterior wall. It appears small; the anterior and superior surfaces of the right lobe are bound by a few old fibrous adhesions. Organ is soft in consistence, the capsule lax. The left lobe is of a peculiar ochre yellow color, dotted with dark-red points. Markings not distinct. The right lobe is mottled dark red to ochre yellow. On section, the left lobe shows same peculiar coloration as on external surface. Right lobe shows irregular areas of ochre yellow alternating with areas dark red in color. Dark red points are scattered thickly over cut surfaces. Normal markings cannot be made out. Gall bladder of normal size, contains a rounded olive-shaped calculus of " mulberry " appearance, 2.3 x 1.7 cm. It is filled with a clear viscous yellowish fluid containing a slight amount of whitish flocculent material. Cystic duct and common bile duct are patulous throughout, papilla of Vater appears normal. There is no evidence of cholecystitis.

Microscopic examination of the liver. — The case examined with the low power shows areas which correspond more or less well with the second case. In this there are areas of hemorrhage in the centers of many of the lobules. In places, chiefly in the centers of

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the lobules, a disappearance of the liver tissue with the collection in these areas of endothelial cells. The liver cells are more extensively preserved. They are all of them intensely fatty, the fat being in very small granules. Certain of these fatty cells have lost their nuclei and appear to be necrotic. There are few polynuclear leucocytes, though more than in the preceding case. In some of the cell areas along with the large epithelioid there are cells chiefly of a plasma character belonging to the lymphoid series. No distinct cell phagocytosis is seen.

In this case also there is an extensive rapid destruction of liver cells with the same process of softening and disappearance as in the preceding case. The necrosis of the cells seems to have been preceded by an enormous formation of fat within them. In this case also the difference between this character of necrosis with liquefaction and the ordinary focal necrosis is striking. In neither of the cases is the necrosis focal. It is general and distributed all over the tissue with very slight difference in degree. In no place in this specimen have the liver cells totally disappeared.

Kidneys: weight, 210 gm. Organs are softened in consistency, stellate veins injected. In section, cortex 0.6 cm. in width; capsule very slightly adherent. The cortex and medullary rays are of an opaque light-yellow color; Malpighian corpuscles appear usually as fine red points, exceptionally as larger opaque yellowish gray granules. Extending into cortical region from the bases of the pyramid are radiating lines of translucent grayish appearance. Line of demarcation between cortex and pyramids is very distinct, the pyramids being dark red in color, their vessel prominent as dark red lines. Whole kidney appears engorged with blood.

Scharlach R. shows large and small fat droplets in

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the epithelial cells of all the urinary tubules throughout their entire extent. The glomeruli show an occasional fine droplet.

Adrenals. — Both adrenals show marked injection of their vessels and appear slightly enlarged.

Bladder. — Mucosa is slightly bile tinged. Otherwise nothing remarkable.

Genital organs. — Tubes and ovaries appear normal. The uterus shows a rounded mass in the muscular wall of the upper fundus region which is grayish white in color, firm, cutting with considerable resistance. The endometrium of fundus region is dark red, slightly thickened. Adherent to it is a long chicken fat clot 0.5 cm. in diameter, extending to the internal os.

Aorta. — The lumbar portion of the vessel shows a few scattered pinpoint areas of slightly elevated, dull grayish appearance, a similar area larger in size, about the orifice of the celiac axis.

Head, not opened.

Case IV. M. McC., age twenty-four, single, housemaid, was admitted April 11, 1908, to the First Medical service of the Boston City Hospital in charge of the writer. The patient was comatose at entrance and the following history was obtained from her physicians, Dr. Merrick and Dr. McLaughlin, of Dorchester.

Previous history. — Her family was a healthy one. She remembered no previous illness. Her mental development was poor. She was considered feeble-minded, but was able to do simple routine work as a laundress. Thorough physical examination seven months ago on admission to an institution gave a normal result.

Six months ago she was delivered of a five months, anencephalic child. Her convalescence was normal; no history of syphilis was obtained and no evidence of

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this disease was found in mother or child. She had never had a previous attack of jaundice.

Present illness. — Nine days before admission to the hospital her digestion was slightly disturbed and mild jaundice appeared. There was no abdominal pain. She had anorexia, vomited a few times and was somewhat weak and depressed. Physical examination on the third day showed nothing but the mild jaundice. The patient was given laxatives and a light diet and advised to keep quiet, and her illness was considered simple catarrhal jaundice. She did not take to her bed till the sixth day of the illness. There was some early variation in the depth of the jaundice, but from this time it increased rapidly and progressively. On the seventh day the patient was quite weak and on the eighth day mildly delirious. A few hemorrhagic papules appeared on the forehead, but there were no other signs of bleeding. There was no fever; the pulse was 96.

The possibility of acute liver atrophy was considered at this time and a careful examination of the hepatic area was made by the above named physicians. The upper border of liver dullness was found in the fifth right interspace and the lower border at the costal margin and the edge was just felt on deep inspiration; nothing abnormal was felt in the gall bladder region. The abdomen was soft and there was no abnormal tenderness. On the ninth day (the day of entrance to the hospital) she became comatose.

Physical examination on the tenth day showed a slender, fairly nourished woman in deep coma with the skin and conjunctivæ colored deep yellow; the pupils were equal and reacted well; the knee jerks were lively; no Babinski or Kernig signs were obtained. The lips were crusted and the teeth covered with blood-stained mucus. The pulse was 90, of good volume and tension.

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The throat was negative, the tongue not protruded; the glands were not enlarged; the neck was not tender. There was occasional tonic spasm of the muscles of the extremities and neck. The heart was normal in size, the first sound was sharp with a suggestion of a presystolic roll and thrill at the apex. The lungs were clear. The abdomen was lax, soft, slightly tympanitic and not tender. The spleen was not felt. There was no ascites or edema of extremities.

The area of liver dullness was much diminished. The upper border was in the normal position in the fifth right interspace in the nipple line. The lower border ran approximately parallel to the right costal margin, *6 or 7 cm. above it*, and the liver dullness was thus reduced to a thin wedge running across the lower front of the right chest, tapering from 6 cm. in width in the anterior axillary line to 2 cm. in width in the midsternal line.

The *blood* on the tenth day was: hemoglobin, 75%; red cells, 6,100,000; white cells, 9,000. In a stained specimen the red cells showed slight achromia and little change in size or shape. There were no blasts. A differential count of the white cells showed: polynuclear leucocytes, 80%; lymphocytes, 12%; large mononuclear, 8%.

The *urine* was collected on the tenth day for twenty-four hours by means of catheterization every four hours, and showed the following characters:

Amount 400 ccm., color dark yellow; specific gravity 1,022. Reaction, strongly acid; albumin, a slight trace; sugar absent; bile pigment present in large amount; albumose and peptone present.

The sediment was deeply bile stained and contained many granular and epithelial casts; many renal cells, some fatty; considerable free fat, vaginal cells; no blood.

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Leucin, much present; tyrosin, much present.

The examination of the urine for leucin and tyrosin was made by the B. napthalin sulphochlorid method.

Quantitative analyses were made showing the total nitrogen excretion in the urine and the proportion excreted as urea and ammonia (using the Kjeldahl and Folin methods). The following results were obtained: Total nitrogen excreted 4.575 gm. and of this 44.8%, or 2.05 gm., was excreted as urea; 12.6%, or 0.515 gm., as ammonia; 2.2%, or 0.101 gm., as uric acid; 7.8%, or 0.359 gm., as creatinine; 32.6%, or 1.57 gm., as residue.

The patient remained in deep coma, taking almost no food, not more than a few teaspoons of milk every hour. There was no further vomiting, or any external bleeding. Occasional tonic spasm of the muscles occurred, but no convulsions. On the day before death the temperature rose to 100.6° and the pulse to 125. The pulse gradually failed in strength and the patient died on the morning of the eleventh day of her illness, the eleventh day after the appearance of the jaundice and the third day after the appearance of the severe cerebral symptoms.

The autopsy was performed three hours post-mortem by Drs. Mallory and Rhea of the Boston City Hospital.

ANATOMICAL DIAGNOSIS.

Acute yellow atrophy of the liver; icterus (general); bronchopneumonia (right lower); fatty degeneration of kidney; subperitoneal hemorrhages (multiple); subpleural hemorrhages (visceral and parietal) (multiple); subpericardial hemorrhages (multiple); congestion and edema of lungs (lower lobe posteriorly); laceration of cervix (bilateral); corpus hemorrhagicum; acne (back) icterus of dura.

Age, twenty-four years. Body, length, 149 cm.

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Body is that of a fairly well developed and fairly well nourished white female. Body, length 149 cm. Rigor mortis is present. There is some lividity of the dependent parts, most marked throughout the lower back. Pupils are 5 mm. and equal. There is no edema. The skin is everywhere dry and is of a very deep yellowish color. This yellowish discoloration is least marked on the hands and the feet, especially on the palmar surfaces of the hands. The conjunctivæ are very deep yellow. Over both cheeks and eyelids are numerous discrete and confluent, light brownish areas which vary from 2 mm. to 6 mm. in diameter. The hair of the eyebrows is very soft and silky. Over the upper part of the back are several discrete, slightly elevated, dark brownish red areas which stand up slightly above the surrounding skin. The centers of some of these areas show small pustules. The external orifices are normal. The abdominal fat measures 3 cm. in thickness. It is firm and of a very bright yellow color.

Peritoneal cavity. — The peritoneum is for the most part smooth and glistening throughout. The underlying tissues are of a light yellow color. The ileocecal fossa is very distinct and measures 2 cm. in depth. The distal 2 cm. of the vermiform appendix rests in this fossa, entering it behind the fold of the peritoneum which forms the right border of the ileocecal fossa. The appendix measures 5 cm. in length, is free from adhesions and has a mesentery to within 6 mm. of its tip. Both iliac fossæ show numerous small, discrete, sharply outlined, oval and round, deep red areas which shine through the peritoneum. Beneath the peritoneum, covering the mesentery and the retroperitoneal tissues, are numerous discrete, round and oval, bright red areas. Similar areas are seen beneath the peritoneum covering the mesentery of the ascending

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and transverse colons. The mesenteric lymph nodes are not increased in size or consistence. On section they are pale. Diaphragm, left fifth rib, right fifth space.

Pleural cavities. — They are free from adhesions. The surfaces are generally smooth and glistening. Beneath the pleura covering the diaphragm on each side are several small, discrete, dark red areas, similar to those seen beneath the peritoneum.

Pericardial cavity. — The pericardial fluid is normal in amount and shows marked yellowish discoloration.

Heart. — Weight 180 gm. The width of the right auricle at its mid-portion is 12 cm. The depth of the right ventricle is 6 cm. The width of the left auricle at its central portion is 11 cm. The depth of the left ventricle is 7 cm. Just beneath the pericardium covering the left ventricle, most marked in the areas where the pericardial fat is in greatest abundance, are several discrete, round and oval, dark red areas, similar to those seen beneath the pleura and beneath the peritoneum. The myocardium is firm and of a uniform slightly yellowish color. This yellowish discoloration is most marked in the immediate vicinity of the larger blood vessels. The endocardium is smooth and glistening throughout. In none of the heart cavities is there any clotted blood except a very small amount between the trabeculæ in the region of the tip of the left ventricle. There is a moderate amount of fluid blood in both ventricles.

Measurements: tricuspid valve, 9 cm.; pulmonary valve, 6 cm.; mitral valve, 8.5 cm.; aortic valve, 5.5 cm.

Lungs. — Left: Just beneath the pleura in the region of the apex, both anteriorly and laterally, are numerous small, discrete, deeply injected areas which are irreg-

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ularly oval to round in shape. These areas extend a very short distance into the underlying lung substance. On section the upper lobe is generally of a light salmon pink color. In its lower anterior portion there are several discrete and confluent, dark red areas which vary from 2 mm. to 3 cm. in diameter. In these areas the lung is less crepitant than elsewhere. On pressure a very dark blood-stained fluid escapes from them. The remainder of the lung is of a light salmon pink color except in the lower posterior portion of the lower lobe, which is generally a dark red in color, and from its cut surface a considerable amount of blood-stained fluid escapes.

Right: In the anterior lower central portion of the lower lobe there is a slightly elevated, sharply outlined, firm area 4 cm. in diameter. On section this stands up somewhat above the surrounding lung tissue, and on pressure numerous pinpoint, light grayish drops of fluid exude. The remainder of the lung is crepitant, slightly less so in the posterior portion, where the lung substance generally is of a dark red color, and a considerable amount of blood-stained fluid escapes. The upper lobe is light salmon pink in color. It is crepitant throughout.

Spleen. — Weight 110 gm. The surface is smooth. On section the pulp is light brownish red in color and of normal consistence. The Malpighian bodies are distinctly visible as small, grayish points. The vessels and trabeculæ are just visible.

Gastro-intestinal tract.— The stomach contains a small amount of undigested liquid food. Its mucous membrane is normal. The small intestine contains thin, bile-stained fecal material. Its mucous membrane is normal. The large intestine contains in its upper portion a small amount of thin bile-stained fluid;

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in its lower portion a moderate amount of firm, dark brown, fecal material. The mucous membrane of the intestinal tract generally is distinctly discolored yellow.

Pancreas. — Normal.

Liver. — Weight 595 gm. Upon opening the abdominal cavity there is no part of the liver visible, it being situated entirely behind the ribs. At the central portion of the right lobe the lower margin of the liver reaches to within 5 cm. of the costal margin. When the liver is removed there is quite a marked tendency for the organ to collapse. Save at the extreme tip, the left lobe can be easily rolled up like a scroll. When rested upon the right lobe with the left lobe pointed upward, this latter portion tends to collapse over the right lobe. Generally the external surface of the liver is light brownish in color and its capsule is thrown into very delicate folds, though there are certain firm areas which are elevated, sharply demarcated from the surrounding liver substance, of deep yellowish color and consist of discrete and confluent areas. The largest is situated at the extreme tip of the left lobe. This area is 5.5 cm. long and 6 cm. broad at its base. Its extreme tip consists of a diffluent area. This diffluent area extends to the right along the course of the upper lobe for 2.5 cm. The remaining 3 cm. of the elevated area at the tip of the left lobe is made up of discrete, elevated, yellowish nodules between which the liver substance is slightly depressed and of a light yellowish red color. There is a discrete, firm, elevated area in the dome of the left lobe. This area measures 4.5 cm. by 6 cm. In general it is similar to the area described above in the extreme tip of the left lobe. Elsewhere throughout the surface there are small, discrete, elevated, firm yellowish areas. On section the liver shows the following picture: The two large elevated

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areas described above, the one situated in the extreme tip of the right lobe and the other in the central portion of the dome of the right lobe, extend down entirely through the liver substance and are quite sharply demarkated from the surrounding parenchyma. They are made up of large confluent and small discrete, distinctly elevated, firm, yellowish areas, the former in their central portion, the latter about their periphery. They are much firmer than the surrounding liver substance and are quite friable. The remainder of the liver is flabby and on section is generally very light brown in color with small, narrow, band-like, pale areas, which interlace, dividing the liver into distinct lobular-like areas. While the elevated yellowish areas are generally confined to the two larger areas described above, there are a few small areas of similar character throughout the remainder of the liver substance. The gall bladder and its ducts are opened *in situ*. The gall bladder contains a small amount of thin, yellowish bile. The bile ducts are patent. The ampulla of Vater is normal. Bile escapes into the duodenum upon pressure of the common bile duct, or the gall bladder.

Kidneys. — Weight 260 gm. On section the cortex is of a pale, distinctly yellowish color and is very sharply demarcated from the pyramids, which are a light brownish red in color. The blood vessels in the cortex and pyramids are slightly injected. Malpighian bodies are distinctly visible as small glistening points.

Adrenals. — Normal.

Bladder. — Is contracted. It contains a small amount of dark-colored urine. The mucous membrane of the bladder is deeply bile stained.

Genital organs. — The cervix is smooth and glistening. Its mucous membrane is light yellowish in color.

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The cervix shows a transverse, bilateral tear. The uterus measures 7.5 cm. long and 1.5 cm. broad at the external os, 1 cm. broad at the internal os and 4 cm. broad at the fundus, between the cornu. The left ovary is normal. The right ovary is slightly increased in size and contains a sharply demarcated, very dark red area 8 mm. in diameter.

Aorta. — It is generally of a deep yellowish color. At the bifurcation it is 2.5 cm. in diameter; at its mid-portion 3.5 cm.; at the lower portion of the descending arch 4 cm. in width. In its lower third it shows a few linear, slightly elevated, slightly yellowish patches.

Organs of neck. — Normal.

Bone marrow. — The bone marrow of the femur is soft, made up of dark red, granular areas embedded in fat. The ribs show a rather small amount of bone marrow. The bony framework of the medulla of the ribs is rather prominent. The bone marrow of the vertebra is light red in color.

Spinal cord. — The subdural fat is distinctly bile stained. The dura is not adherent. On section the markings of the cord are distinct. There are no gross pathological lesions demonstrable.

Head: weight, brain 1,270 gm. Head is covered by a thick growth of long brown hair. The calvarium is negative. The dura shows a decided light orange color and is moderately adherent to the calvarium. On section the brain is apparently normal.

Middle ears. — Normal.

Microscopic Examination.— The heart shows slight fatty degeneration. The spleen, pancreas, adrenal, gastro-intestinal tract and central nervous system are practically normal. The kidney shows very extreme fatty degeneration of tubules of all types. The glomeruli show no changes

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Liver. — Sections were taken from numerous regions. All show very marked degeneration; those from the firmer, yellow, elevated areas, noted at autopsy, show less marked changes. The general picture in the section from the more normal regions shows large and small islands of liver cells widely separated by a tissue containing only blood spaces and cells of inflammatory origin. The large groups of liver cells, in some instances, show a lobular arrangement. The smaller groups show no trace of normal structure. All of the liver cells show marked changes. There is an increase in size with marked vacuolation, and at the periphery of the groups the vacuolation is extreme and the shapes assumed are irregular and often grotesque. The bile capillaries are prominent and filled either with a densely stained eosin material, or inspissated bile. In the surrounding tissue no trace of liver cells is to be found. There are many large, mononuclear cells, some of which are pigmented yellow, while others are phagocytic, and numerous cells of the lymphoid series. These cells lie in spaces between injected blood spaces which evidently correspond to the sinusoids of the liver.

In the regions of most marked destruction of the liver tissue, there are only a few small groups of cells recognizable as liver cells. There remain only marked injected blood spaces, probably corresponding to the sinusoids. Between the blood spaces there are many pigmented and phagocytic mononuclear cells. In places there seems to be an increase of connective tissue, but this is not confirmed by the connective tissue stain. Within small groups of liver cells there are numerous polymorphonuclear leucocytes. None of the liver cells show the dense hyaline change of the protoplasm seen in other forms of degeneration. Everywhere throughout these portions of the liver,

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there are many branching bile ducts, in which many evidences of direct nuclear division can be found. Mitoses were not found in the liver cells, though some cells have a denser basic staining, compact protoplasm like that of cells found in regenerating liver tissue. No definite hemorrhages are present. The Scharlach R. stain for fat shows that the vacuolated liver cells contain fat.

This case presents the same general conditions which have been described in the preceding cases. The stage of the process is earlier than that of the first case and probably later than either the second or third case, as regeneration is taking place, at least from the bile ducts.

CHEMICAL EXAMINATION.—The following tissues were sent to Dr. Carl L. Alsberg, of the Harvard Medical School, for chemical examination: Heart, heart's blood, lung, spleen, liver, kidney, adrenal, intestinal contents. A part of the results of chemical analysis of the liver are given. The other analyses were not completed in time to be included in this paper. They will be reported later.

The liver was examined chemically to determine the distribution of nitrogen according to the method of Hauseman. Osborne's modification. (*Journal of the American Chemical Society*, 1903, xxv, 323.) The analyses were made in duplicate. The per cent of the different forms of nitrogen is as follows (the nitrogen under the fifth heading does not come under the heading of monamino, diamino or amid nitrogen. Osborne simply reports it as nitrogen in the Mg O_2H_2 precipitate):

Liver analysis. — Total nitrogen, 2.66%; amid nitrogen, 0.18%; monamino nitrogen, 1.62%; diamino nitrogen, 0.55%; nitrogen in the precipitate obtained

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by digestion with acid and addition of excess of Mg O_3 H_2, 0.31%.

The diamino nitrogen in this case is not so low as is sometimes found in cases of autolysis.

CLINICAL SUMMARY OF THESE FOUR CASES.

Occurrence. — Two of our patients were men and two women. The disease is, however, almost twice as common in women as in men, the usual proportion of incidence being 8 women to 5 men. (Quincke.) The patients were of an age (twenty-three, twenty-four, thirty-two, thirty-six) when the disease most commonly appears. All four of our cases developed in the winter time, but season is not considered an important factor.

Etiology. — The preliminary stages were like simple catarrhal or other benign jaundice. Minkowsky has expressed the opinion that the difference between simple benign jaundice and the rapidly fatal type is simply one of degree of intensity of action of the same or similar factors upon the same tissue, and that no sharp distinction can be drawn. Every jaundice, no matter what its cause, may lead to hepatic insufficiency and end in acute atrophy, and the tendency to the severe form of the disease depends on the lack of resistance of the organism as well as upon the intensity of the effect of the poison.

It is, however, fair to suppose that the sudden outburst of severe symptoms is not a sign of the entrance of some new causal factor into a simple case; but in reality the chemical changes which

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produce these symptoms have been preparing for some time, as in uremia and diabetic coma, and the illness has been actually grave from the start.

Certain infections, especially syphilis, play a part in etiology. One of our patients was in the second stage of syphilis when the acute atrophy occurred. This is fairly common. Senator has collected 20 such cases. The question has been raised whether the syphilitic poison or the mercury used in its treatment was the cause of the liver necrosis.

There is no definite evidence in our cases of the development of poisons from ordinary food or of the eating of poisonous substances, such as mushrooms, or of acute alcoholism. A careful analysis of the intestinal contents and liver of two of our cases showed that phosphorus was absent.

The direct importance of bacteria in this disease is very doubtful. Cultures in our cases were either sterile or apparently without significance as is usually the case.

The disease in our patients appeared in otherwise healthy livers, as usually happens, though it may be superimposed on other liver disease, such as cirrhosis, bile stasis and fatty degeneration.

The question of etiology will be more fully discussed under the heading, "Nature of the Disease."

Pathological anatomy. — The liver in all the cases showed a characteristic reduction to one

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half or almost one third the normal size and weight. The normal weight of the liver is 1,500 to 1,800 gm. In our cases it was 730, 600, 960 and 595 gm. respectively. It was flaccid, flattened, folded, and dropped backward unless held by adhesions as in the third case. The cut surface was yellowish red or yellow, mottled with or alternating with large or small red areas. The markings were usually indistinct. The yellow color is not due to fatty degeneration, for this is not the chief change, and in fact fat may be almost entirely absent. Taylor found in a liver which he examined that there was no increase of fat over the normal amount. The chemical analysis of the liver in our second case showed that the amount of fat and lipoids was very much less than normal. The yellow color is due chiefly if not wholly to bilirubin.

The condition is one of intense destruction of the liver tissue different in character from the ordinary necrosis of liver cells. The cells seem to soften and disappear almost entirely by solution, leaving behind connective tissue enclosing endothelial cells and a more or less granular material. The cell masses lose their outline, and have not the sharp acidophilic character nor the refraction of ordinary necrotic liver cells.

In none of the cases was the necrosis focal. It was general and distributed all over the tissue with very slight differences in degree. In the third case the necrosis of the cells seems to have been preceded by an enormous formation of fat

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within them. Fat was almost entirely absent in the other cases.

The first case differed from the others in the fact that it was of somewhat longer duration, fifteen days instead of seven or eleven, and the destructive process was not so extensive and had almost or entirely ceased. The dominant feature was a regeneration to replace the destruction of liver cells. The regeneration of liver tissue was taking place in two ways. In one way by the direct formation of liver cells from other liver cells by division of nuclei, in the other by a process similar to that of embryonic liver formation by the development of undifferentiated epithelial tissue similar in character to the bile ducts and from which the future liver cells develop. The enormous number of epithelial cells which were present were assisting in the process of repair, these cells being phagocytic and engaged in the removal of necrotic and broken down tissue. The presence of bile in the capillaries might be taken as an indication of the very great activity of the remaining liver cells.

This case is especially interesting from its relation to other diseases of the liver. It forms a transition stage in acute and subacute forms of hepatic cirrhosis. Had the destruction of liver tissue not been so profound this case might have developed into some one of the peculiar forms of cirrhosis with atypical lobulation.

In the fourth case also regeneration of liver tissue was in progress to replace destroyed liver

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	Urine amount ccm.	Total nitrogen (gm. per cent).	Urea nitrogen (gm. per cent).	NH_3 nitrogen (gm, per cent.)	Total nitrogen.	Urea, nitrogen.	NH_3 nitrogen.	Uric acid nitrogen.	Residue nitrogen.
I,	960	7.40	4.64	1.61	100%	62%	22.9%	1.6%	13.5%
II,	780	9.87	4.32	2.48	100%	44%	25.%		31.0%
III,					100%*	69.2%	17.%		13.8%
IV,	400	4.575	2.05	0.515	100%	44.8%	12.6%	2.2%	32.6%
mal,	1,500				100%	84–87%	2–5%	1–3%	7–10%

The percentages in this case are based upon a sample including almost the whole twenty-four-hour amount of urine; total amount could not be collected.

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The purin bases (Salkowski method) were determined quantitatively in the first and fourth cases and were not found increased as they often are from increased nuclear destruction, or lack of decomposition of uric acid.

Prognosis. — The disease is a very fatal one, and the outlook is worse the earlier the cerebral symptoms appear. The prognosis in the individual case depends upon the degree of disturbance of the central nervous system. Rapid decrease in liver area, and leucin and tyrosin in the urine usually precede death by only a few days. The presence of hemorrhages is a very unfavorable sign. The state of the kidneys is very important in prognosis. Free diuresis is very necessary to avoid an accumulation of toxic products of metabolism. The grave symptoms of the second stage usually appear simultaneously with a marked reduction in the amount of urine and a great decrease in the nitrogen excretion, which must be considered a sign of retention of poisonous substances in the body.

The possibility of recovery from this disease cannot at present be denied. There is no reason why the injury to the liver should not stop before the liver tissue has been completely destroyed, and when the process of destruction stops rapid regeneration occurs. This regeneration may conceivably go on till more or less complete restoration of liver function and general health is reached.

Our first case showed an extensive process of regeneration of liver tissue and the fourth case a

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considerable degree of regeneration. The amount of regeneration of liver tissue bears a close relation to the rapidity and violence of the toxemia in our four cases. The longer the patient survived his toxemia, the greater the liver regeneration; in the first case, fifteen days' illness, extensive regeneration; in the fourth case, eleven days' illness, moderate regeneration; in the second and third cases, seven days' illness, no regeneration of liver tissue. Other fatal cases in the literature have shown these same regenerative changes, and a considerable number of cases of recovery, now between 20 and 30, have been collected and reported by Wirsung, Senator, von Jaksch, Albu and others.

Diagnosis.— Early diagnosis from a practical clinical standpoint seems almost impossible. Simple benign jaundice is so common and acute atrophy of the liver so rare, that to subject every simple case to elaborate quantitative analyses to determine whether or not it seemed likely to develop acute atrophy of the liver, would be an enormous labor which would bear little fruit.

From a practical standpoint the nervous symptoms were the first guide to the diagnosis. Any unusual disturbances of the general nervous system appearing in acute jaundice should rouse our suspicions of this serious disease. The correct diagnosis was not made, or even suspected, in any of our cases, until the appearance of the second stage.

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The decrease in the area of liver dullness which was so striking and characteristic in all the cases did not appear in the two cases which were under continuous observation till the second stage of the disease within two or three days, at most, before death. Even the presence of adhesions in the third case between the upper surface of the liver and the diaphragm did not prevent the reduction in the area of dullness, though under some circumstances they do obscure the evidence of decrease in size.

The presence of leucin and tyrosin in the urine formerly was considered pathognomonic of the disease. We know now, however, that they may occur in the urine in any condition in which there is much destruction of tissue in the body, but in no other condition in so large amount as is present in acute liver atrophy. They have a certain value in diagnosis, but this has been greatly exaggerated, in my opinion, and is in reality very small from a practical point of view. Their appearance is usually late in the disease, not before the second stage.

The simple methods of detection are unreliable and the accurate methods elaborate and long. If an accurate test is made in the second stage of the disease, as it usually is, it can rarely be completed before the patient dies and has no part in the antemortem diagnosis. The simplest method of detection is examination of the urinary sediment after evaporation of the urine to 1-10 its volume and the addition of alcohol. This microscopical diagnosis

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by means of crystals is a rough and unreliable method and should always be confirmed by chemical tests. Tyrosin needles must not be confused with bilirubin or calcium phosphate crystals. Leucin spheres must be distinguished from urates. This is often difficult and it is wise to remove the urates by precipitation with lead acetate and remove the latter by hydrogen sulphide before examining the urine for crystals.

No simple chemical test had been devised at the time the earlier cases were studied, and the best present chemical methods of analysis for leucin and tyrosin are only qualitative and only moderately delicate; a decided disturbance of liver metabolism may occur without causing their appearance in amount sufficient for detection. The methods of analysis are much too elaborate for the clinician. They require the experience of an expert chemist and their description is outside the scope of this paper. They will be found in the textbooks on biological chemistry. One of the best ways of examination is by the B-naptha-lin-sulphochlorid method which was used in our later cases, Nos. 2 and 4.

Estimation of the relative amounts of the nitrogenous substances excreted in the urine, such as urea, ammonia and the residual nitrogen, is of much more value in diagnosis. When no peptones are present in the urine the residual nitrogen is made up chiefly of amino acids, such as alanin, cystin, etc., in addition to leucin and tyrosin. All these substances are intermediate products of

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nitrogenous metabolism, and the other amino acids have an equal significance with leucin and tyrosin in this disease. The exact quantitative estimation of this residual nitrogen, chiefly composed of amino acids, is a better way of measuring the disturbance of liver metabolism than a test for the presence of leucin and tyrosin by a rough and unreliable microscopic examination or by a merely qualitative method which is complicated, but not very delicate.

Even the disturbance of liver function, which we assume to be shown by the increased excretion of ammonia and a lessened excretion of urea in the urine, must be used with caution as a diagnostic sign on account of its variability and dependence on other factors, such as acidosis.

The actual character of the nitrogen excretion in these cases, as well as the presence or absence of leucin and tyrosin, were determined by analyses made *after the death of the patients* on urine previously collected, and while very interesting and important *they played no part in the ante-mortem diagnosis. This will usually be the case.*

In two cases the urine was tested for leucin and tyrosin only by examination of the crystalline sediment after evaporation to 1-10 volume and precipitation with alcohol. Leucin and tyrosin were both present in one case and both absent in the other. In two cases the urine was tested by the much more accurate B-napthalin-sulphochlorid method, and leucin and tyrosin were both present in each case.

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The presence in the urine of oxy-acids derived from the amido acids, of lactic acid, of albumoses, and of purin bodies from the increased destruction of nuclei cannot be said to have any special diagnostic significance.

Severe cerebral symptoms appearing with jaundice have been termed *icterus gravis*. This condition may be present in quite a variety of pathological conditions, chiefly severe acute infections, such as pneumonia, sepsis, typhoid, malaria, peritonitis, etc. They can usually be excluded by the absence of fever, the intensity of the jaundice, the very small area of liver dullness, the urinary changes, and the absence of specific signs, such as changes in the lungs (pneumonia) or the blood (malaria, typhoid).

The diagnosis from acute phosphorus poisoning may be peculiarly difficult; fortunately it rarely has to be made in this country. The illness is of very short duration, the jaundice usually less marked, and the hemorrhages larger.

When the course of the illness is fairly typical, as it was in our four cases, any one having the clinical picture of the disease well in mind would have little difficulty in diagnosis when the second stage was reached. The diagnosis is much more likely to be missed because the disease is not considered on account of its rarity, rather than because it was carefully considered and then ruled out.

Treatment in our cases, and of the disease in general, is most discouraging and unsatisfactory.

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The results of treatment seem trifling and hopelessly ineffective in the face of so violent and fatal a malady. Something may possibly be expected of treatment in the prodromal stage which is practically that of catarrhal jaundice. Our first effort should be to remove any harmful material from the digestive tract by calomel or salines. Laxatives also stimulate peristalsis in the bile passages and help to empty them. Plenty of drinking water will help to dilute the bile and lessen its consistency, and the absorption of water from the bowels will help to dilute those substances which might damage the liver in their passage through it. Its value as a diuretic and means of washing out poisonous substances from the body is very important. More active diuretics, caffein, diuretin, are occasionally useful.

We also try to lessen the work of the diseased organ by an appropriate diet; limit fats and give them only in emulsion (milk); carbohydrates, the principal food, are given in easily digestible form.

In the second stage the same principle of removing poisonous substances, if possible, by the bowel and urine, holds good. Where the patient's condition will not permit abundant administration of water by stomach or bowel, subcutanous injections of salt solution must be used to restore sufficient diuresis. Otherwise, the treatment is symptomatic, sedatives, such as bromides for restlessness and delirium, ice pills, cocaine, etc., for vomiting, and stimulants for heart weakness.

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NATURE OF THE DISEASE.

Acute yellow atrophy holds a peculiar position among diseases of the liver on account of the great speed and degree of change in the liver cells. We have the striking picture of a large solid organ rapidly decreasing in size by the self-digestion of its cells and the appearance in the urine and blood of products of proteid digestion (leucin, tyrosin, etc.). The course of the disease has raised so many interesting questions regarding the functions of the liver and metabolism in general and its anatomical relation to other diseases of the liver, that it has attracted much greater interest and been far more carefully studied than other diseases of equal rarity.

Recent work on autolysis, the self-digestion of body cells, by Salkowski, Taylor, Jacoby and others, has thrown much light on the process of liver atrophy. Salkowski has shown that any aseptically preserved organ can undergo autolysis or self-digestion by its own ferments, if kept at body temperature, and produces substances similar to those of ordinary intestinal digestion including leucin and tyrosin. Autolysis has been found to be important in many pathological conditions, such as the absorption of exudates and of aseptic necrosed tissue. The necrosis in this disease apparently differs from ordinary necrosis in the rapidity and completeness of absorption of the dead cells. It resembles somewhat the resolution of a pneumonia.

The rapid disappearance of over one half of a

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large solid organ like the liver within a few days strongly suggests a process of self-digestion of necrotic liver cells by their own ferments. This is explained by the supposition that the original poison causing the process has a very specific action on the liver cells and destroys their life without injuring the proteolytic ferments which they contain, and thus self-digestion occurs. This view that a cell may be killed and also be able to digest itself is borne out by the autolysis of tissue in infarctions. The autolysis and absorption in the liver would go on much more rapidly because the circulation is good and removes the products as fast as they are formed. On chemical analysis of the liver itself, in our second and fourth cases the distribution of nitrogen precipitable and nonprecipitable by phosphotungstic acid shows very clearly the presence of marked autolysis.

The poison must affect the other cells of the body to a much less degree than the liver, so that it is possible for the patient to survive the liver necrosis for a time, during which absorption goes on until there is finally so great a loss of liver tissue and functions that general toxemia results.

On the other hand, liver extirpation in animals by Nencki and Pawlow, Saleskin and Zaleski and others have shown that in certain cases, in spite of the absence of the liver, an abundant formation of urea occurs, and no appreciable change in the proportion of ammonia to the total

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